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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1954

THE RESULTS OF CHEMOTHERAPY IN URINARY INFECTIONS

BY

L. P. GARROD, M.D., F.R.C.P. R. A. SHOOTER, M.D.

AND

M. P. CURWEN, M.A.

(From the Departments of Pathology and of Medical Statistics, St. Bartholomew's Hospital, London)

Twenty-five years ago the only available urinary antiseptic was hexamine. Since then the ketogenic diet, mandelic acid, the sulphonamides, and various antibiotics have successively become available, providing opportunities, or so it would seem, for the successful treatment of almost any infection which can arise. How successfully this wealth of therapeutic resources has been applied it is difficult to judge: in particular, further data seem desirable on the results of treatment with drugs more recently introduced and now in almost exclusive use.

Many reports describe the immediate good results which follow the treatment of infections of the urinary tract with modern antibacterial drugs. The longer the period after treatment, however, the more frequent is relapse or reinfection, and Stenderup *et al.* (1952) express a widely held view when they remark that, considering the present resources of chemotherapy, the results of treatment of urinary infections are not as good as might be expected. Stenderup and his colleagues, who treated 181 patients, found that relapse or reinfection occurred not only in patients with abnormal urinary tracts or a past history of infection but also, although less frequently, in patients with no obvious complicating factors.

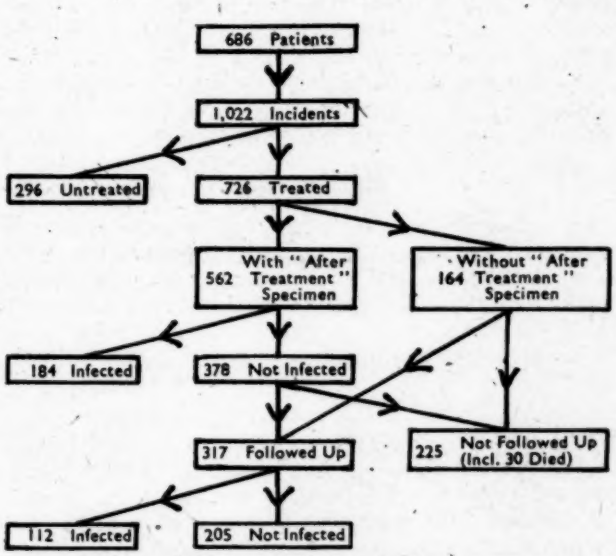
The importance of obstruction in the ultimate outcome of treatment was clearly shown by Rhoads *et al.* (1952), in the treatment of 325 patients, more than 75% of whom had demonstrable urinary obstruction. They found that, while rather more than half their patients had sterile urine after treatment, only some 11% were permanently cured, and these were patients without obstruction originally or in whom the obstruction had been corrected.

Patients with infections of the urinary tract are numerous, and their study provides the laboratory with a considerable volume of work. This investigation was designed to take advantage of such routine material with a view to discovering how often laboratory sensitivity tests are likely to foretell the result of treatment when the patient is treated with a drug to which the infecting organism is sensitive.

Composition of Series

The series includes nearly all the adult patients with diagnosed urinary infections seen in the hospital between September, 1952, and August, 1953, and is presented in outline in the accompanying Diagram. Some patients were treated by chemotherapy more than once during this period, and the 1,022 incidents derived from 686 patients represent the total number of patients seen either for the first time or after the failure of a previous course of treatment.

Patients seen more than once were included in the series only if presenting with a fresh infection or if still needing treatment for an infection which had failed to respond, and were not automatically included to swell the total figures. This has inevitably led to the repeated



Structure of the investigation

inclusion of patients with the same *condition* (for example, urinary tract abnormality), but less often to the inclusion of patients with the same *infection* (for example, infection with *Bacterium coli*). As will be seen in the results, treatment may fail to sterilize the urine although the original organism may often be replaced by another. Of the 686 patients, 500 figure only once, the remaining 186 patients being responsible for 522 incidents, an average of 2.8 incidents per patient.

Most of the after-treatment specimens of urine were examined within five days of the end of treatment, and

the majority of follow-up specimens two to four months later. All specimens were collected by catheter in females and aseptically in males. No attempt was made to influence clinicians in their choice of treatment except in so far as they were influenced by a report of sensitivity tests. Clinical information, which was not specially recorded for this survey, was taken from the patient's notes after discharge and, with the laboratory findings, was subsequently analysed by means of Hollerith punch cards. Tables I and II show the departments of the hospital from which the patients were drawn and the age and sex distribution of all the patient-incidents encountered, together with the duration of symptoms, the number of patients with a previous history of urinary tract infection and with known urinary tract abnormalities, and the number treated by chemotherapy.

TABLE I.—*Composition of the Series by Departments*

Department	In-patients	Out-patients
General medicine	181	109
General surgery	298	146
Gynaecology and obstetrics	230	30
Other	5	23
Total	714	308

TABLE II.—*Composition of the Series by Age, Sex, Clinical History, Duration of Symptoms, and Number Treated*

	Sex	Total	Age †			Duration of Symptoms ‡			Treated by Chemotherapy
			Less than 35	35–64	65 or More	Less than 2 Weeks	2–8 Weeks	9 weeks or More	
With U.T.A.*	M	297	18	134	145	10	15	256	162 (55%)
	F	101	31	43	24	3	4	83	76 (75%)
Without U.T.A. but with history of previous infection	M	76	2	56	17	2	13	40	51 (67%)
	F	263	63	145	54	46	32	126	197 (75%)
Without U.T.A. and no history of previous infection	M	51	10	30	11	19	17	3	30 (59%)
	F	234	65	132	37	154	30	22	210 (90%)
Total	M	424	30	220	173	31	45	299	243 (57%)
	F	598	159	320	115	203	66	231	483 (81%)

* U.T.A. = Urinary tract abnormality.
† Omitting 5 patients of unknown age.
‡ Omitting 147 patients for whom this was not recorded.

Dosage Schemes

Dosage schemes varied, but only in a few instances did they appear to be inadequate. Of patients who were given procaine penicillin 83% received 600,000 units or more daily, and of those receiving crystalline penicillin 94% were given 1,000,000 units or more daily. Of patients receiving streptomycin, 28% had 2 g. or more daily, while 98% had 1 g. or more. At least 1 g. of chlortetracycline was given daily to 98% of the patients being treated with this drug. A daily dose of 3 g. or more was given to 79% of patients receiving sulphonamides.

Analysis of the length of treatment of patients from whom an after-treatment specimen of urine was obtained, and who were treated with a single drug, showed that when penicillin was used it was given for at least four days in 90% of cases, aureomycin for at least four days in 93%, and sulphonamides for at least four days in 95%. All the patients treated with streptomycin received it for at least two days.

Laboratory Methods

All sensitivity tests were done by the agar diffusion method in primary culture. For tests with antibiotics three holes 8 mm. in diameter were cut with a sterile cork-borer in a blood-agar plate previously dried, and two in another. The plates were inoculated by uniform spreading with a bent glass rod of a 2-mm. loopful of urine and the cups were filled with solutions containing penicillin 100 units/ml., streptomycin, chlortetracycline ("aureomycin"), oxytetracycline ("terramycin"), and chloramphenicol 250 μg./ml. Chlortetracycline solution was made daily; the remainder at intervals of one to two weeks, with storage at +4° C.

Sulphonamide sensitivity tests were done similarly, except that a special medium was used. This consisted of normal male urine, 1% glucose, and 2% agar, adjusted to *p*H 7, to which 5% of blood was added. On this appropriate medium, which is free from sulphonamide inhibitors, urinary organisms grew satisfactorily. Holes in this medium were filled with solutions of sulphadiazine, sulphathiazole, sulphadimidine (all sodium salts), and sulphacetamide, each of a concentration of 25 mg./100 ml. Sensitivities to all four drugs were measured for the first 254 organisms. It was found that in all but four instances the radii of the inhibition zones were, within experimental limits, in the same decreasing order, the mean values being sulphathiazole 7.3 mm., sulphadiazine 7.2 mm., sulphadimidine 5.8 mm., sulphacetamide 3.4 mm.

Thereafter the tests were done with sulphathiazole only, this being chosen in preference to sulphadiazine, which has a closely equivalent overall activity, because sulphathiazole was the only one of these drugs to which staphylococci were ever at all sensitive.

Reading of Results

The sensitivities to both antibiotics and sulphonamides were read as 0, +, ++, or +++ according to the width of the zone of inhibition produced. The approximate equivalents of these readings in terms of the minimum inhibitory concentrations were determined by testing a series of organisms in parallel by a tube dilution method, with the results in Table III. It is not pretended that this method is accurate or even that it was applied with strict accuracy: the width of the inhibition zones is so much affected by several factors, notably profusion of growth, that minute measurements of zones in such cultures is pointless. On the other hand, it is well suited by its simplicity and rapidity for routine use on a large scale and is unlikely to lead to gross error in experienced hands.

TABLE III.—*Quantitative Significance of Degrees of Sensitivity Estimated*

Degree of Sensitivity	Radius of Inhibition Zone	Equivalent Minimum Inhibitory Concentration*					
		Sulphathiazole	Penicillin	Streptomycin	Chlortetracycline	Chloramphenicol	Oxytetracycline
0	—mm.	>16	>10	>10	>20	>20	>20
+	2–5 ,,	4–8	5–10	2·5	5–10	10	10
++	6–10 ,,	2	2–5	1·2	2·5	2·5–5	2·5–5
+++	>11 ,,	<1	<1	<0·6	<0·6–1·2	1·2	<0·6–1·2

* For sulphathiazole in mg./100 ml.; for penicillin in units/ml.; for remainder in μg./ml.

Bacteriological Findings

Of the 1,022 infections studied 881 were due to a single organism, 133 to 2, 7 to 3, and 1 to 4. The numbers of

10 identified species studied are stated in Table IV. It can be seen from this table that *Streptococcus faecalis* commonly occurred in association with another organism, 38% of infections with this organism being multiple; *Bact. coli*, on the other hand, commonly occurs alone, only 11% of infections being multiple. Further analysis of the types of infection occurring together revealed nothing of apparent significance.

TABLE IV.—*Composition of the Series by Species* of Organism and Sex of Patient*

	Total		Male		Female	
	Single	Multiple	Single	Multiple	Single	Multiple
Bact. coli	368	47	83	13	285	34
Bact. coli intermediate	39	10	20	7	19	3
Bact. aerogenes	17	7	9	3	8	4
Paracolon bacilli	56	27	50	26	6	1
P. vulgaris	62	19	22	11	40	8
P. morgani	39	25	37	24	2	1
Ps. pyocyanea	44	16	29	12	15	4
Str. faecalis	105	63	27	27	78	36
Staph. pyogenes	28	19	16	10	12	9
Staph. albus	66	18	27	7	39	11
Other organisms	57	39	24	28	33	11
Total infections	881	141	344	80	537	61

* Lactose-fermenting coliform bacilli were identified as follows: *Bact. coli* methyl red+, growth in citrate−; *Bact. coli* intermediate M.R.+; citrate+; *Bact. aerogenes* M.R.−, citrate +. Non-lactose-fermenting coliform bacilli were classified by mannite fermentation, indole production, and formation of H_2S, paracolon bacilli being mannite±, indole+, and H_2S −; *P. morgani* mannite−, indole±, and H_2S+. The remaining species were identifiable by more obvious characters, except that coagulase production was used to distinguish the two species of staphylococci.

The distribution of organisms by sex is shown in the same table. A notable feature here is the preponderance of females in *Bact. coli* infections, and to a smaller extent in those due to *Str. faecalis*. On the other hand, paracolon bacilli, *Proteus morgani*, and *Pseudomonas pyocyanea* occur more commonly in males than in females. These differences are presumably related to the route by which bacteria reach the urinary tract. The common organisms in the female are those predominating in the lower bowel, and an ascending infection from the ano-genital region would explain this. Such a mechanism is unlikely in the male, but alternative routes which would account for the difference in flora could only, in the present state of knowledge, be suggested on a purely speculative basis.

The percentages of strains of all identified organisms found in culture to be resistant to each drug are stated in Table V.

TABLE V.—*Percentages of Organisms Resistant (0 or +) to Six Drugs*

	Total No. of Orgs.*	Percentage resistant (0 or +) to:					
		Penicillin	Streptomycin	Chlortetracycline	Chloramphenicol	Oxytetracycline	Sulphathiazole
Bact. coli	414	99	10	13	9	5	11
Bact. coli intermediate	49	98	45	23	19	11	43
Bact. aerogenes	24	96	21	21	17	17	38
Paracolon bacilli	83	100	90	72	75	67	94
P. vulgaris	81	52	23	89	22	89	28
P. morgani	63	52	90	78	32	76	100
Ps. pyocyanea	60	100	73	85	93	80	97
Str. faecalis	167	17	87	18	9	18	100
Staph. pyogenes	47	77	40	9	9	9	100
Staph. albus	83	19	25	12	10	13	85

* The figures in this table do not exactly correspond with those in Table IV as a small number of organisms were not tested for sensitivity.

Some entries in this table merely illustrate natural resistance, such as that of *Ps. pyocyanea* to penicillin and of *Str. faecalis* to sulphonamides. Others afford some guide to the likelihood of success in treatment and presumably indicate the extent to which resistance has been acquired in consequence of past use of drugs in this country. The most generally resistant organisms are paracolon bacilli, *P. morgani* and *Ps. pyocyanea*, and this property, as will be seen later, is reflected in therapeutic results. Both *P. morgani* and *P. vulgaris* are unlike other Gram-negative species in being frequently sensitive to penicillin. Most strains *of Staphylococcus pyogenes* are penicillin-resistant but usually sensitive to chlortetracycline, oxytetracycline, and chloramphenicol. Resistance to these drugs is also less common among Gram-negative bacilli than it has been reported to be in the United States (Romansky *et al.*, 1951) and Australia (Thomson, 1952), but the results of widespread habituation are evident in the findings for streptomycin and sulphathiazole.

An indication of the changes in sensitivity during the period of treatment is given by a study of the 103 organisms which were recorded as being present in the urine before and immediately after treatment, and for most of which two sets of sensitivity tests to the six drugs were carried out. Out of the 593 pairs of readings there was no change in 427 (72%), a *decrease* in sensitivity in 90 (15%), and an *increase* in 76 (13%). These findings are analysed in more detail in Table VI, which shows the original sensitivity and the degree of change—two steps being, for instance, a change from 0 to ++. It will be seen that the majority of changes were of only one step; technical faults or misinterpretation may be responsible for most of these. *Decreases* in sensitivity of more than one step were mostly due to the drug used in treatment, often streptomycin. *Increases* may sometimes have been actual (increased sensitivity to an antibiotic after exposure to another has repeatedly been observed): another possibility is the elimination of the original strain and the substitution of another.

TABLE VI.—*Changes in Sensitivity to 6 Drugs of 103 Organisms Tested Before and Immediately After Treatment*

Initial Sensitivity	Total	No Change	Increased Sensitivity			Decreased Sensitivity		
			One Step	Two Steps	Three Steps	One Step	Two Steps	Three Steps
0	267	246	7	11	3	—	—	—
+	28	11	9	3	—	5	—	—
++	151	78	43	—	—	12	18	—
+++	147	92	—	—	—	32	9	14
Total*	593	427	59	14	3	49	27	14

* In 25 instances one of the pair of sensitivities was not tested, and these are omitted from the table.

Results of Treatment

The criterion of cure used in this investigation was the elimination of all organisms from the urine, and it has been applied to the results immediately after treatment and to the follow-up results. An after-treatment specimen of urine was obtained from 562 of the 726 patients treated with chemotherapy, and, although the number of patients from whom no specimen was received is larger than might have been hoped, knowledge of the circumstances and a comparison of some of the factors recorded induce us to believe that this has led to no gross selection. Follow-up specimens were examined from 317 of the 512 treated patients known to be alive and who either were free from infection immediately after treatment or from whom no after-treatment specimen was obtained. No attempt was made to follow up the 296 untreated patients or the 184 who were still infected after treatment.

Results in Relation to the Patient's Condition

As past experience and a preliminary examination of our results showed that the condition of the patient was the main factor in determining the outcome of treatment, treated patients have been divided into three categories—those with urinary tract abnormalities, those without abnormalities but with a past history of urinary infection, and the remainder in whom no abnormality was demonstrated and who gave no history of previous urinary infection. In the first and second groups the same patient may appear as two or more separate incidents, but the third group, by definition, cannot include more than one incident for each patient. Table VII shows the number in each group together with their ages,

TABLE VII.—*Immediate Cure Rates of 562 Treated Patients, Showing Age, Sex, Clinical History, etc.*

	Sex	Total	Age †			Duration of Symptoms ‡			Catheterized Within Previous Month	Cured
			Less than 35	35–64	65 or More	Less than 2 Weeks	2–8 Weeks	9 Weeks or More		
With U.T.A.*	M	116	7	51	58	4	11	97	79	39 (34%)
	F	55	19	22	14	1	2	49	35	32 (58%)
Without U.T.A. but with history of previous infection	M	34	—	27	6	—	6	19	13	16 (47%)
	F	159	32	93	34	31	20	79	100	118 (74%)
Without U.T.A. and no history of previous infection	M	20	3	14	3	3	10	1	1	16 (80%)
	F	178	54	101	23	120	21	17	118	157 (88%)
Total	M	170	10	92	67	12	27	117	93	71 (42%)
	F	392	105	216	71	152	43	145	253	307 (78%)

* U.T.A.=Urinary tract abnormality.
† Omitting 1 patient of unknown age.
‡ Omitting 66 patients for whom this was not recorded.

the proportion catheterized in the preceding month, the length of the current infection, and the immediate results of treatment.

It was at once clear that we were dealing with groups of uneven size and that direct comparison of the results of treatment of males and females will be invalid. The men were older, and those with urinary tract abnormalities predominated, while the largest groups of women were those with no abnormality, many of these (144) being gynaecological patients with a post-operative infection. The adverse effect of abnormalities or a previous infection is, however, demonstrated in each group.

Results in Relation to the Infecting Organism

Table VIII shows the immediate cure rates for multiple infections and for infections due to single organisms when the latter were treated with a drug to which the organism was sensitive or found subsequently to be resistant. The most striking feature is perhaps the number of patients

TABLE VIII.—*Immediate Cure Rates of Treated Patients by Sensitivity of Organism to Drug Used in Treatment*

	Sex	Single Organisms *		Multiple Organisms
		Sensitive (++ or +++)	Resistant (0 or +)	
With U.T.A.	M	22/47 (47%)	5/29 (17%)	4/24 (17%)
	F	27/44 (61%)	2/4	1/3
Without U.T.A. but history of previous infection	M,F	108/143 (75%)	11/21 (52%)	8/18 (44%)
Without U.T.A. and no history of previous infection	M,F	144/162 (89%)	8/10	19/23 (83%)

* Omitting 34 patients with a single organism but treated with multiple drugs.

cured even although treated with an inappropriate drug. The figures are small but presumably represent the natural cure rate, although it should be pointed out that six of the patients with no adverse history and treated with an inappropriate drug had coccal infections, which, as will be seen, are most easily cured.

Table IX shows the cure rate of infections due to individual species of organisms when these were sensitive to the drug. The better response of coccal infections is in part due to the fact that they were more frequent among the clinically favourable cases, but even when allowance

TABLE IX.—*Immediate Cure Rates of Treated Patients by Species of Organism**

Str. faecalis	52/58 (90%)
Staph. pyogenes and *albus*	31/38 (82%)
Coliform †	188/244 (77%)
P. vulgaris	18/30 (60%)
P. morgani	2/11
Paracolon bacilli	6/13
Ps. pyocyanea	5/10
Other organisms	18/26 (69%)

* Omitting multiple organisms, and organisms resistant (0 or +) to the drug used in treatment.
† *Bact. coli*, *Bact. coli* (intermediate), and *Bact. aerogenes*.

is made for this by using the three clinical categories, the same relationship between the cure rate for the three types of organism holds good. This is shown in Table X, which shows in addition that the corresponding rate for resistant organisms also follows the same pattern.

TABLE X.—*Immediate Cure Rates of Treated Patients* by Type of Organism and Clinical History*

	Type of Organism		
	Coccal	Coliform	Others
Sensitive organisms:			
Patients with U.T.A.	15/21 (71%)	28/49 (57%)	16/41 (39%)
Patients without U.T.A. but history of previous infection	16/19 (84%)	79/104 (76%)	20/31 (65%)
Patients without U.T.A. and no history of previous infection	52/56 (93%)	81/91 (89%)	13/18 (72%)
Resistant organisms:			
All patients	13/19 (68%)	7/17 (41%)	6/28 (21%)

* Omitting patients with multiple organisms.

Results in Relation to the Drug Used

Analysis of the results of treatment according to the drug used has failed to produce clear evidence of the superiority of one drug to another. Judging by the immediate cure rates, without taking other factors into consideration, "sulphatriad," sulphadimidine, and penicillin were most successful, curing 85, 82, and 81% of patients respectively. Sulphathiazole cured 78%, while of the patients treated with chlortetracycline, streptomycin, and sulphacetamide, 76, 69, and 50% respectively were cured. Bald presentation in this form is, however, misleading. Nearly all the patients, for instance, to whom sulphacetamide was given had abnormalities of the renal tract, and some of the apparent failures of aureomycin can also be accounted for in this way. The figures for streptomycin may also be fallacious, as there was no certainty that this drug was always withheld until the urine had been made alkaline.

Elimination of Specific Organisms from the Urine

As the aim of treatment is the cure of the patient, it is unrealistic to assess chemotherapy by its ability to remove a specific organism from the urine without at the same time producing a sterile urine. It should, however, be mentioned that of the 148 patients with a single infection whose urine was not sterilized, in as many as 68 (46%) the original organism was eliminated only to be replaced by another. It has not been possible to establish any clear connexion between this phenomenon and the clinical condition. It was as liable to happen in uncomplicated infections as in others, and, what is more, occurred as often when the original organism was resistant to the drug used in treatment as when it was sensitive.

Infections due to Str. faecalis

Evidence was obtained that catheterization and previous treatment with sulphonamides increased the likelihood of a urinary infection being due to *Str. faecalis*.

Of 157 women with urinary infections due to a single organism who had been given sulphonamides in the month

prior to examination and who had also been catheterized, 45 (29%) were infected with *Str. faecalis*, as were 3 of the 11 patients who had been given sulphonamides only. Twenty-seven of the 189 women (14%) who had been catheterized but had not received sulphonamides developed a *Str. faecalis* infection, whereas only 3 of 169 (2%) who had neither been catheterized nor received sulphonamides were so infected. The figures for men showed a similar trend.

Follow-up Results

The failure to obtain a follow-up specimen from a comparatively large number of patients was disappointing, but there is no reason to suppose that it materially altered the results. Patients not followed included many of the older patients (particularly if living outside London), and to this extent the cure rates may be too high. On the other hand, the inclusion of many of the more complicated cases would tend to depress the rate.

Table XI shows the patient's condition to be of prime importance and the main factor in determining the cure rate. Even among uncomplicated cases, however, and to a greater extent among the patients with a past history of infection but no demonstrable abnormalities, an appreciable number were found to be infected at the follow-up.

TABLE XI.—*Comparison of Immediate and Follow-up Results*

		Immediate		Follow-up *	
	Sex	No. of Patients	No. with Sterile Urine	No. of Patients	No. with Sterile Urine
Patients with U.T.A.	M	116	39	58	15
	F	55	32	27	7
Patients without U.T.A. but history of previous infection	M	34	16	16	10
	F	159	118	79	51
Patients without U.T.A. and no history of previous infection	M	20	16	11	9
	F	178	157	126	113

* The figures in these columns *exclude* patients with an infected urine after treatment but *include* some from whom no after-treatment specimen was obtained. This accounts for the fact that, in one instance, the number of patients followed up is greater than the number shown as sterile in the previous column.

There were a few patients whose urine after treatment was sterile but nevertheless contained pus. No evidence was obtained that these patients were more likely to be infected at follow-up than patients whose urine contained neither pus nor organisms.

Discussion

This paper is based on the practice of this hospital over 11 months, as seen from the laboratory, and while this viewpoint has advantages it also has disadvantages which will already be apparent. Some 80 doctors were able to contribute patients to the survey, and inevitably treatment varied with personal preferences. The most serious result of this is that the frequency with which patients were seen after treatment has varied and the results are less clear-cut than they might have been if all the patients had been treated in accordance with a common plan. Nevertheless certain facts have emerged.

The most striking is the confirmation of previous reports that, despite the undoubted efficacy of modern antibacterial drugs, chemotherapy usually fails to sterilize the urine of patients with abnormalities of the urinary tract, and that in the absence of a demonstrable abnormality a history of previous infection also reduces the likelihood of cure, although to a lesser degree. While in some instances the drug could hardly be blamed for this failure, as the original organism was eliminated only to be replaced by another, in general it presumably represents the inability of the sulphonamides and antibiotics to deal effectively with bacteria in the circumstances peculiar to an obstructed renal tract.

Treatment of patients with uncomplicated infections is more satisfactory, but even here an appreciable number were found to be still infected immediately after treatment, and of those with sterile urine at this time a few were again infected some months later. All these groups of patients demonstrated the value from the patient's point of view of a re-examination some months after apparently successful treatment.

It was also clear from the patients' notes that some infections were relatively or completely symptomless and that under the conditions of a busy out-patient department it was not always possible to exclude urinary infection by naked-eye inspection of a sample of urine. If these observations apply to patients treated in other places, it would seem reasonable to suggest that to avoid chronic renal infection with its attendant dangers the cure of patients treated for urinary tract infections should be confirmed by microscopical examination of the urine both after treatment and again some months later.

Turning to what must be regarded as less important factors, there seems to be little to choose between the six drugs most commonly used in this investigation—sulphatriad, sulphadimidine, sulphathiazole, penicillin, streptomycin, and chlortetracycline. On grounds both of efficacy and expense, and possibly of lack of toxicity, the sulphonamides clearly keep their place in the treatment of urinary infections. The position of sulphacetamide is uncertain. Its activity *in vitro* suggests that it would be the least effective of the sulphonamides, and superficially our results support this. As, however, only a small number of patients were treated with it, and most of these had obstructive lesions, the finding that sulphacetamide had the lowest cure rate of all the drugs employed cannot be accepted as a true indication of its value.

It is clear (Table IX) that prognosis depends much on the species of organism, coccal infections responding best, those due to *Bact. coli* and closely related species well, whereas other organisms can less often be eliminated. There is also a clear relationship (Table VIII) between the sensitivity of the organism and the outcome of treatment, although some patients recover despite the use of an inappropriate drug. Laboratory examination, including sensitivity tests, can evidently improve the chances of successful treatment substantially. It distinguishes in the first place between coccal and coliform infections, the appropriate treatments for which differ unless a "broad spectrum" antibiotic is used: secondly, it takes account of strain variations in sensitivity among individual species. As may be seen from Table V, the number of strains, even of commoner bacteria, abnormally resistant to sulphonamides and to those antibiotics particularly which have been longer in use, is far from negligible.

Summary

Clinical and laboratory findings in 1,022 urinary infections occurring in 686 adult patients are given with particular reference to the presence of urinary tract abnormalities and a past history of urinary infection, and to the species of organism(s) present and their sensitivity to sulphonamides and to five antibiotics.

Of these infections 726 were treated with chemotherapy and the results of treatment assessed by examination of after-treatment and follow-up specimens of urine, using absence of organisms from the urine as the criterion of cure. After-treatment specimens obtained from 562 patients showed that, while the prognosis was good in patients with no urinary tract abnormalities and no history of urinary infection (16/20 males and 157/178 females being cured), it was indifferent in patients with a previous history of urinary infection (16/34 males and 118/159 females being cured) and poor in patients with a definite urinary tract abnormality (only 39/116 males and 32/55 females being cured). The follow-up findings confirmed this and showed the necessity for examining the urine some months after treatment if the results are to be assessed correctly.

Among less important factors affecting cure, coccal infections were shown to respond best, those due to *Bact. coli* and *Bact. aerogenes* well, whereas infections due to *Proteus, Ps. pyocyanea,* and paracolon bacilli were more resistant to treatment. There was a clear relationship between the *in vitro* sensitivity of the organism and the outcome of treatment, and the use of laboratory sensitivity tests is advocated to avoid the prescription of inappropriate drugs. For most species identification only is no longer sufficient. No clear evidence was obtained that any one of the drugs used most often (sulphatriad, sulphadimidine, sulphathiazole, penicillin, streptomycin, and chlortetracycline) was superior to the others.

We are grateful to our clinical colleagues for permitting us to use the material on which this investigation is based, and particularly to the Medical and Surgical Registrars for their collaboration. Among those who have been involved in heavy additional work we wish particularly to thank Miss E. J. Armour for tracing patients' records, and Mr. R. Andrew, Miss M. Rhodes, and Miss P. M. Waterworth for laboratory assistance.

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FAILURE OF SULPHONAMIDES TO PREVENT URINARY INFECTIONS AFTER VAGINAL SURGERY

BY

M. P. DURHAM, M.B., F.R.C.S., M.R.C.O.G.

R. A. SHOOTER, M.D.

AND

M. P. CURWEN, M.A.

(From the Departments of Gynaecology and Obstetrics, Pathology, and Medical Statistics, St. Bartholomew's Hospital, London)

Urinary infections occur frequently in patients undergoing vaginal operations, and sulphonamides are often given for their prevention. As the majority of these infections are due to *Streptococcus faecalis,* an organism resistant to sulphonamides, or to coliform bacilli, many of which nowadays are also resistant, the value of this form of treatment is likely to be limited. This paper is an account of a trial designed to test this conclusion.

Procedure

The trial lasted from February 1, 1953, until January 31, 1954, and was conducted in two wards (A and B). For the first three months patients admitted to ward A for vaginal operations (detailed in Table I for the whole series) were given 1 g. of "sulphatriad" three times a day for the first seven days after operation, patients in ward B receiving no such special treatment. At the end of three months the arrangement was reversed, patients in ward B receiving sulphatriad, while no prophylactic treatment was given to patients in ward A, and this alternation was continued for one year. Administrative reasons precluded a closer method of control, such as the use of alternate patients.

Catheter specimens of urine were collected from patients from both wards in the theatre before operation and again on the tenth post-operative day, or earlier if indicated by the patient's clinical condition. In all, 117 patients were involved. Of these, 15 were excluded (6 infected before operation, 8 because specimens of urine were not examined, and 1 who was treated with penicillin for a wound infection), leaving in the trial the 102 patients described in Table I.

TABLE I.—*Composition of the Series*

	Test Group (Sulphonamide Given)	Control Group (No Sulphonamide)
Number of patients	60	42
Mean age	53 years	52 years
Age range	28–76 years	32–73 years
Ward A	33	18
„ B	27	24
Diagnosis		
Prolapse with stress incontinence	25	20
„ without „ „	24	17
Stress incontinence	6	2
Menorrhagia	4	3
Leucoplakia	1	—
Operation		
Colporrhaphy	47	36
Vaginal hysterectomy	10	6
Sling operation	2	—
Vulvectomy	1	—

Post-operative Catheterization

Three different procedures were adopted. Some patients were allowed to pass water unaided, or were catheterized if necessary. Others were left with an indwelling Malecot catheter, which was spigoted, the spigot being removed at approximately three-hourly intervals. The remainder were left with an indwelling catheter which drained into a jar containing 1/1,000 acriflavine. For several patients both methods of indwelling catheterization were used, but except in four instances it has been possible to classify the patients according to the type of catheterization predominantly employed. Table II shows how patients treated by these three methods were divided between the two wards and between the test and control groups. On an average indwelling catheters were retained for four days, after which patients were catheterized twice daily for three more days. The patient subject to most manipulation was one who, in addition to five days' drainage by an indwelling catheter, required catheterization 24 times. At the other end of the scale, of the patients left initially to pass water unaided, six never required catheterization.

TABLE II.—*Methods of Catheterization*

	Total	Ward A	Ward B	Test Group	Control Group
Indwelling catheter:					
With drain	53	36	17	30	23
„ spigot	28	6	22	16	12
No indwelling catheter	17	6	11	11	6
Not classified	4	3	1	3	1

Results

Table III shows the proportions of test and control patients with urine free from bacteria after operation, set out by wards and according to methods of catheterization. It

TABLE III.—*Proportions of Patients Free from Infection after Operation*

	Test Group (Sulphonamide Given)	Control Group (No Sulphonamide)
Total	9/60 (15%)	3/42 (7%)
Ward A	2/33	0/18
„ B	7/27	3/24
Indwelling catheter		
With drain	2/30	0/23
„ spigot	3/16	1/12
No indwelling catheter	4/11	2/6

is clear that the large majority in both groups became infected; no significance can be ascribed to the slightly better results in the test group. From the point of view of post-operative treatment, patients with no indwelling catheter did a little better than those so treated, but it should be pointed out that six of these patients were not catheterized, and of these five were free from infection. Of the remaining 11 who were repeatedly catheterized, only one remained free.

Effect of Prophylactic Sulphonamide on Type of Infection

Table IV shows the organisms found in post-operative specimens of urine from the two groups of patients. It demonstrates that, although sulphonamides may prevent infection

TABLE IV.—*Organisms Found in Post-operative Specimens of Urine*

	Test Group (Sulphonamide Given)	Control Group (No Sulphonamide)
• Coliform bacilli	6	22
• *Str. faecalis*	36	12
Coliform bacilli + *Str. faecalis*	2	2
Other organisms	7	3
Total	51	39

• Figures for coliform bacilli and *Str. faecalis* include cases with one of these organisms together with another, such as *Staph. pyogenes*.

with coliform bacilli, it is at the expense of infections due to *Str. faecalis*, as infections with this organism are much more likely to occur in patients given prophylactic sulphonamides. No evidence was obtained that the patient's clinical course was altered. Of the patients given sulphonamides 29% developed a post-operative temperature of 100° F. (37.8° C.) or more: in the control group a similar temperature was recorded for 31%.

Discussion

Tables I and II show that the two groups of patients in this trial are not exactly comparable, the most important variation being in the number of patients in the two wards. This led to differences in post-operative management and possibly in nursing technique, but does not alter the conclusion that urinary infection followed operation with regularity whatever regime was used. In the circumstances described here, prophylactic treatment with sulphonamides has failed to prevent urinary infections after vaginal operations.

No support was obtained for the view that post-operative urinary infections are common in gynaecological patients because patients are frequently infected before operation. Pre-operative infection was found in only 6 out of the 113 patients from whom specimens were obtained. The use of an indwelling catheter for several days, or repeated catheterization, necessitated by mechanical factors, presumably accounts for the high rate of infection.

Summary

A clinical trial is described in which 60 patients undergoing vaginal operations, who were given 1 g. of "sulphatriad" three times a day for the first seven post-operative days, were compared with 42 controls who had no prophylactic treatment.

In both groups the urine of a large majority of the patients became infected.

Str. faecalis infections were relatively *more* frequent, and coliform bacilli *less* frequent in the sulphatriad group than in the controls.

Our thanks are due to Mr. John Beattie, Mr. Donald Fraser, and Mr. John Howkins, whose patients were the subject of the investigation, and to the two ward sisters and the nursing staff for their invaluable co-operation.

THE EFFECT OF AN INDWELLING CATHETER ON THE BACTERIOLOGY OF THE MALE URETHRA AND BLADDER

BY

RALPH SHACKMAN, M.B., B.S., F.R.C.S.

AND

DAVID MESSENT, M.B., B.S., F.R.C.S.

From the Department of Surgery, Postgraduate Medical School of London, Hammersmith Hospital

Various bacteria inhabit the normal urethra of the male. Thomson-Walker (1914), quoting Petit and Wasserman (1891), has stated that Löffler's bacillus, *Streptobacillus urethrae, Bact. coli, Staph. albus, Staph. aureus,* and *Staph. citreus* are the most constant organisms, while Harkness (1950) has stated that staphylococci, micrococci, diphtheroids, haemolytic streptococci, *Str. faecalis,* and "Rosenthal's large diplococcus" are the organisms most often found. These bacteria exist without any clinical or microscopical evidence of urethritis, and are presumably saprophytic.

When an indwelling urethral catheter is retained for any length of time a urethritis, less severe when latex rubber catheters are used, almost always results. The urethral organisms are then said to be commonly *Staph. albus* and haemolytic streptococci, and sometimes *Str. faecalis* (Harkness, 1950).

An indwelling catheter also results in the vast majority of cases, and despite administration of sulphonamides and antibiotics, in a cystitis of varying degree. Topley and Wilson (1946) state in general that the commonest bacteria found in cases of cystitis are *Bact. coli, Bact. aerogenes, Pr. vulgaris, Str. faecalis, Ps. pyocyanea,* and staphylococci, but the bladder organisms in the specific circumstances when indwelling catheters are retained are not recorded in the literature available to us.

To investigate the nature of the bacterial flora which occurs in the urethra and bladder in the presence of an indwelling catheter, and to determine the relationship, if any, between the organisms coincident at the two sites, we took a series of urethral swabs and catheter specimens of urine for bacteriological examination from 20 patients at daily or two-daily intervals. In 6 of the 20 patients the studies were made before prostatectomy; in the remaining 14 patients the studies were made after prostatectomy. The urethral swabs were taken from the fossa navicularis; the urine specimens were taken simultaneously from the distal end of the catheter.

To supplement the investigation, we also determined, by similar methods, the nature of the bacterial flora of (i) the urethra of 9 urological and 4 non-urological male patients not previously instrumented or catheterized, (ii) the recently instrumented urethra in 11 patients, and (iii) the urine passed either shortly before (midstream) or withdrawn at the time of insertion of an indwelling urethral catheter in 18 patients.

The bacteriological cultures were made on blood agar and MacConkey agar plates, and were incubated aerobically at 37° C. for 24 hours. No anaerobic cultures were made.

Coagulase-positive staphylococci are referred to as *Staph. aureus,* and micrococci and coagulase-negative staphylococci are together referred to as *Staph. albus.*

Results

(i) Cultures of Urethral Swabs from the Urethra of Male Patients Not Previously Instrumented or Catheterized

Bacteriological culture of single urethral swabs from 13 non-instrumented and non-catheterized patients, 9 urological and 4 non-urological, proved to be sterile in 3 instances and grew various organisms in 10 (Table I). In 6 of the patients single organisms were cultured, while in 4 multiple organisms were grown.

TABLE I.—*Cultures of Urethral Swabs from the Urethra of Male Patients not Previously Instrumented or Catheterized*

Case No.		Case No.	
1	Sterile	15	*Staph. albus*
2	*Pr. vulgaris*	16	Sterile
3	Sterile	21	*Staph. albus, Str. faecalis*
6	Diphtheroids	22	*Staph. albus*, diphtheroids
7	*Staph. albus*	23	*Bact. coli*, diphtheroids
11	*Staph. aureus*	24	*Str. faecalis*
14	*Staph. albus*, diphtheroids		

Cases 1–16 inclusive are urological, non-instrumented, and non-catheterized patients. Cases 21–24 inclusive are non-urological patients.

Analysis of all the organisms cultured from single urethral swabs of the 13 patients showed *Staph. albus* on 5 occasions, diphtheroids on 4, *Str. faecalis* on 2, *Staph. aureus* on 1, *Bact. coli* on 1, and a *Proteus* organism on 1.

(ii) Cultures of Urethral Swabs from Recently Instrumented Patients

Bacteriological cultures of single urethral swabs from 11 patients, all urological and recently instrumented, proved to be sterile in one instance and grew various organisms in 10 (Table II). In 5 of the patients single organisms were cultured, while in 5 multiple organisms were grown.

TABLE II.—*Cultures of Urethral Swabs from Recently Instrumented Patients*

Case No.		Case No.	
4	*Staph. aureus*, haem. strep.	13	*Bact. coli, Str. faecalis*
5	*Str. faecalis*	17	*Staph. aureus, Bact. coli*
8	*Staph. albus*, diphtheroids	18	Diphtheroids
9	*Staph. albus*	19	Sterile
10	*Str. faecalis*	20	*Staph. albus*
12	*Staph. albus, Staph. aureus*		

Analysis of all the organisms cultured from single urethral swabs of the 11 patients showed *Staph. albus* on 4 occasions, *Str. faecalis* on 3, *Staph. aureus* on 3, *Bact. coli* on 2, diphtheroids on 2, and a haemolytic streptococcus on 1.

(iii) Cultures of Bladder Urines Taken Either Shortly Before or at the Time of Insertion of an Indwelling Catheter

Bacteriological culture of single specimens of bladder urines of 18 patients taken either shortly before (midstream specimens) or at the time of insertion of an indwelling urethral catheter proved to be sterile in 8 instances and grew organisms in 10 (Table III). In 7 of the patients, single organisms were cultured, while in 3 multiple organisms were grown.

Analysis of all the organisms cultured from the single specimens of bladder urine of the 18 patients showed *Bact. coli* on 4 occasions, *Staph. aureus* on 3, *Str. faecalis* on 2, *Staph. albus* on 2, a paracolon bacillus on 1, and diphtheroids on 1.

(iv) Cultures of Urethral Swabs from Patients with Indwelling Catheters

(*a*) *Before Prostatectomy.*—Bacteriological cultures of urethral swabs from 6 patients with indwelling urethral catheters before prostatectomy grew organisms, sooner or later, in every case (Table III). In the cultures of four (an arbitrary number taken for convenience) consecutive swabs taken from each patient at daily or two-daily intervals following catheterization, there were single organisms on 10 occasions and multiple organisms on 11 (in three instances the cultures were sterile).

Analysis of all the organisms cultured from the four consecutive urethral swabs of the 6 patients showed *Staph. albus* on 16 occasions, *Staph. aureus* on 4, diphtheroids on 4, *Proteus* organisms on 4 (*vulgaris* 3, *morgagni* 1), haemolytic streptococci on 2, paracolon bacilli on 2, *Bact. coli* on 1, and *Str. faecalis* on 1. In 3 of the 6 patients there was a degree of constancy of organisms in the four consecutive swabs.

(*b*) *After Prostatectomy.*—Bacteriological cultures of urethral swabs from 14 patients with indwelling urethral catheters after prostatectomy grew organisms, sooner or later, in every case. In the cultures of four consecutive swabs taken from each patient at daily or two-daily intervals after operation, there were single organisms on 25 occasions and multiple organisms on 26 (in five instances the cultures were sterile). Analysis of all the organisms cultured from four consecutive swabs of the 14 patients showed *Staph. albus* on 27 occasions, *Bact. coli* on 24, *Str. faecalis* on 13, *Staph. aureus* on 12, *Proteus* on 7 (*morgagni* 4, *vulgaris* 3), diphtheroids on 3, *Bact. aerogenes* on 2, *Ps. pyocyanea* on 1, and a paracolon on 1. In 9 of the 14 patients there was a degree of constancy of organisms in the four consecutive swabs.

(v) Cultures of Bladder Urines from Patients with Indwelling Catheters

(*a*) *Before Prostatectomy.*—As shown in Table III, bacteriological cultures of the bladder urines from the 6 patients with indwelling urethral catheters before prostatectomy grew organisms in every case within a day or so of insertion of the catheters: 4 of the 6 patients had sterile urines at the time the catheters were passed. In the cultures of four consecutive specimens taken from each patient at daily or two-daily intervals there were single organisms on 11 occasions and multiple organisms on 10 (in three instances the cultures were sterile). Analysis of all the organisms cultured from the four consecutive specimens of the 6 patients showed *Bact. coli* on 10 occasions, *Str. faecalis* on 9, *Ps. pyocyanea* on 4, *Staph. albus* on 4, *Proteus* on 3 (*morgagni* 2, *vulgaris* 1), a paracolon bacillus on 2, *Staph. aureus* on 1, and *Str. viridans* on 1. In 4 of the 6 patients there was a degree of constancy of organisms in the four consecutive specimens.

(*b*) *After Prostatectomy.*—Bacteriological cultures of the bladder urines from the 14 patients with indwelling urethral catheters after prostatectomy grew organisms in every case within a day or so of the insertion of the catheter. In the cultures of four consecutive specimens taken from each patient, at daily or two-daily intervals, there were single organisms on 26 occasions and multiple organisms on 19 (in 11 instances the cultures were sterile). Analysis of all the organisms cultured from the four consecutive specimens of the 14 patients showed *Bact. coli* on 19 occasions, *Proteus* on 17 (*morgagni* 12, *vulgaris* 5), *Str. faecalis* on 9, a paracolon bacillus on 8, *Staph. aureus* on 7, *Ps. pyocyanea* on 5, *Bact. aerogenes* on 3, *Staph. albus* on 3, and diphtheroids on 1. In 12 of the 14 patients there was a degree of constancy of organisms in the four consecutive specimens.

Discussion

The present study virtually confirms the statements of previous authors (Thomson-Walker, 1914; Harkness, 1950) that the saprophytic organisms of the normal male urethra are staphylococci, *Str. faecalis*, diphtheroids, *Bact. coli*, *Str. viridans*, and bacilli of the *Proteus* group. Our observations also suggest that recent instrumentation does not materially affect the nature of this bacterial flora.

Before prostatectomy we found the commonest urethral organism, when an indwelling urethral catheter was retained, was *Staph. albus*. This confirms, in part, the statement of Harkness (1950). We did not, however, commonly find haemolytic streptococci or *Str. viridans*, while we did find diphtheroids, *Proteus* strains, *Staph. aureus*, paracolon bacilli, and *Bact. coli*.

After prostatectomy we still found that *Staph. albus* was the commonest urethral organism, but that *Bact. coli* was almost as common. It was not unusual to find *Str. faecalis*, *Staph. aureus*, and *Proteus* strains, while diphtheroids, *Bact*

aerogenes, Ps. pyocyanea, and paracolon bacilli were present on occasion. We did not find haemolytic streptococci.

The main difference, therefore, between the bacterial flora of the urethra before and after prostatectomy was the marked development of *Bact. coli* after that operation.

Before prostatectomy we found the commonest organism in the bladder urine when an indwelling catheter was retained was *Bact. coli. Str. faecalis* was almost as common, while *Ps. pyocyanea, Staph. albus, Proteus* strains, *Staph. aureus,* paracolon bacilli, and *Str. viridans* also occurred.

After prostatectomy we still found that *Bact. coli* was the commonest organism in the bladder urine, but that a *Proteus* strain was almost as common. *Str. faecalis,* paracolon bacilli, *Staph. aureus,* and *Ps. pyocyanea* were not uncommon, while *Bact. aerogenes, Staph. albus,* and diphtheroids also occurred.

TABLE III.—*Bacteriological Cultures of Urethral and Bladder Urine Organisms*

Case No.						
1	Urethra	(C) *Staph. albus*	*Staph. albus*	*Staph. albus*	*Staph. albus*	
	Bladder	Sterile	*Staph. albus*	*Bact. coli; Pr. vulgaris*	*Bact. coli*	
2	Urethra	(C) *Pr. vulgaris*	*Staph. albus;* haemolytic streptococci, Group B	Sterile	*Staph. albus;* diphtheroids; *Pr. vulgaris*	
	Bladder	Sterile	Sterile	*Staph. albus*	*Staph. albus*	
3	Urethra	Sterile	(C) *Staph. albus*	*Staph. albus*	Sterile	*Staph. albus;* diphtheroids
	Bladder	Sterile	*Str. faecalis; Pr. morgagni*	*Str. faecalis; Ps. pyocyanea*	*Str. faecalis; Ps. pyocyanea*	*Str. faecalis; Ps. pyocyanea*
4	Urethra	(I.C.) ●x *Staph. aureus;* haemolytic streptococci, Group C	●x Sterile	●x *Staph. albus*	●x *Staph. albus; Staph. aureus*	
	Bladder	*Staph. aureus*	*Str. faecalis; Ps. pyocyanea*	Paracolon	*Pr. morgagni*	
5	Urethra	(I) *Str. faecalis*	(C) Paracolon	*Staph. albus; Staph. aureus ; Pr. vulgaris*	*Pr. morgagni*	*Staph. aureus;* paracolon
	Bladder	*Bact. coli*	*Bact. coli*	*Bact. coli*	*Bact. coli*	*Bact. coli*
6	Urethra	Diphtheroids	(C) *Staph. albus;* diphtheroids	*Staph. albus;* diphtheroids	*Staph. albus; Bact. coli*	*Staph. albus; Str. faecalis*
	Bladder	Sterile	*Str. faecalis; Str. viridans; Bact. coli*	*Str. faecalis; Bact. coli*	*Str. faecalis; Bact. coli*	*Staph. albus; Str. faecalis;* paracolon; *Bact. coli*
7	Urethra	*Staph. albus*	(P.C.) ●x *Staph. albus*	●x *Staph. albus*	●x *Staph. albus*	●x *Staph. albus*
	Bladder	*Staph. albus*	Sterile	Sterile	*Bact. coli; Pr. morgagni*	*Bact. coli; Pr. morgagni*
8	Urethra	(I) *Staph. albus ;* diphtheroids	(P.C.) ●x Sterile	●x *Ps. pyocyanea*	●x Sterile	●x *Staph. albus*
	Bladder	*Staph. aureus*	Sterile	*Ps. pyocyanea*	*Pr. morgagni; Str. faecalis*	*Pr. morgagni; Ps. pyocyanea*
9	Urethra	(I) *Staph. albus*	(P.C.) ●x *Staph. albus; Str. faecalis*	●x *Str. faecalis; Bact. coli*	●x *Staph. albus; Str. faecalis; Bact. coli*	●x *Staph. albus; Bact. coli*
	Bladder	Sterile	Sterile	Sterile	*Staph. albus*	*Staph. albus*
10	Urethra	(I) *Str. faecalis*	(P.C.) x *Str. faecalis; Bact. coli*	x *Bact. coli*	x *Str. faecalis; Bact. coli*	x *Str. faecalis; Bact. coli*
	Bladder	*Str. faecalis; Bact. coli*	Diphtheroids; *Bact. coli*	*Bact. aerogenes*	*Bact. aerogenes; Ps. pyocyanea*	*Bact. aerogenes; Ps. pyocyanea*
11	Urethra	*Str. viridans;* diphtheroids	(I.P.C.) ●x *Staph. albus*	●x *Staph. aureus*	●x *Staph. aureus*	●x *Staph. aureus*
	Bladder	*Staph. aureus*	Sterile	*Pr. morgagni*	Paracolon	*Pr. morgagni*
12	Urethra	(I) *Staph. aureus; Staph. albus*	(P.C.) ●○ *Staph. albus*	●○ *Staph. albus ;* diphtheroids	●○ Sterile	●○ *Staph. albus; Str. faecalis*
	Bladder	Sterile	*Pr. morgagni*	*Pr. morgagni; Ps.pyocyanea; Str.faecalis*	*Pr. morgagni; Str. faecalis*	*Pr. morgagni; Str. faecalis*
13	Urethra	(I) *Str. faecalis; Bact. coli*	(P.C.) ●□ *Str. faecalis; Bact. coli*	●□ *Staph. aureus; Str. faecalis; Bact. coli*	●□ *Staph. aureus; Bact. coli*	●□ *Staph. aureus; Bact. coli*
	Bladder	*Bact. coli*	*Bact. coli*	*Staph. albus; Bact. coli*	*Staph. aureus; Bact. coli*	*Staph. aureus; Bact. coli*
14	Urethra	*Staph. albus;* diphtheroids	(P.C.) ●□ Sterile	●□ *Staph. albus*	●□ *Staph. albus; Staph. aureus;* diphtheroids	●□ *Staph. albus; Staph. aureus; Bact. coli;* diphtheroids
	Bladder	*Staph. albus;* diphtheroids	Sterile	*Bact. coli*	Paracolon	*Bact. coli*
15	Urethra	*Staph. albus*	(I.P.C.) ●□ *Staph. aureus*	●□ *Staph. albus*	●□ *Staph. albus*	●□ *Staph. albus*
	Bladder	Paracolon	Sterile	*Pr. morgagni*	Sterile	Paracolon
16	Urethra	Sterile	(P.C.) ●□ *Staph. albus*	●□ *Bact. coli*	●□ Paracolon	●□ *Staph. albus; Staph. aureus*
	Bladder	Sterile	*Str. faecalis;* paracolon	Paracolon	Paracolon	Paracolon
17	Urethra	(I) *Staph. aureus; Bact. coli*	(P.C.) ● x *Bact. coli*	● x *Bact. coli*	● x *Staph. albus; Bact. coli*	● x *Bact. coli*
	Bladder	Sterile	*Bact. coli*	*Bact. coli*	*Bact. coli*	*Str. faecalis; Bact. coli*
18	Urethra	(I) Diphtheroids	(P.C.) x *Staph. albus; Bact. coli*	x *Staph. aureus; Str. faecalis; Bact. coli; Pr. vulgaris*	x *Staph. albus; Bact. coli; Pr. vulgaris*	x *Str. faecalis; Bact. coli; Pr. vulgaris*
	Bladder	*Str. faecalis; Bact. coli*	*Bact. coli; Pr. morgagni*	*Staph. aureus*	*Str. faecalis; Bact. coli; Pr. vulgaris*	*Str. faecalis; Bact. coli; Pr. vulgaris*
19	Urethra	(I.P.C.) ● x Sterile	● x *Staph. albus; Staph. aureus; Bact. aerogenes*	● x *Staph. albus ; Bact. coli; Bact. aerogenes; Pr. vulgaris; Str.faecalis*	● x *Str. faecalis; Bact. coli*	
	Bladder	*Str. faecalis; Bact. coli*	*Staph. aureus; Pr. vulgaris*	*Staph. aureus; Bact. coli; Pr. vulgaris*	Paracolon; *Bact. coli; Pr. vulgaris*	
20	Urethra	(I.P.C.) □ *Staph. albus*	□ *Staph. albus; Pr. morgagni*	□ *Pr. morgagni*	□ *Bact. coli; Pr. morgagni*	
	Bladder	Sterile	Sterile	*Bact. coli*	*Bact. coli*	

C=insertion of catheter; P.C.=prostatectomy and insertion of catheter; I=instrumentation; ●=penicillin; x=sulphonamides; □=streptomycin; ○=chloromycetin. The post-catheter cultures were from specimens taken at daily or two-daily intervals.

The main difference, therefore, between the bacterial flora of the bladder urine before and after prostatectomy was the marked development of *Proteus* strains after that procedure. Presence or absence of organisms in the bladder urine before retention of an indwelling catheter did not appear materially to affect the nature of the bacterial flora which subsequently developed after retention of the catheter.

Comparing the organisms which occur coincidently in the urethra and the bladder urine in the presence of an indwelling urethral catheter before prostatectomy, it is seen that there is little relationship between the bacterial flora of the two sites. *Staph. albus, Staph. aureus,* diphtheroids, and *Proteus* strains predominate in the urethra, whereas *Bact. coli* and *Str. faecalis* predominate in the bladder urine in these circumstances.

After prostatectomy, however, it is seen that there is a closer relationship. For there is a high incidence of *Bact. coli* in both the urethra and the bladder urine in these circumstances. Nevertheless, the relationship is not by any means complete, because there is also a high incidence of *Staph. albus, Str. faecalis,* and *Staph. aureus* in the urethra, whereas there is a high incidence of *Proteus, Str. faecalis,* paracolon bacilli, and *Ps. pyocyanea* in the bladder urine.

Summary

The nature of the bacterial flora which occurs coincidently in the urethra and bladder in the presence of an indwelling urethral catheter has been investigated in patients before and after prostatectomy.

The bacterial flora of (*a*) the previously non-instrumented and non-catheterized male urethra, (*b*) the recently instrumented male urethra, and (*c*) the urine passed either shortly before (midstream) or withdrawn at the time of insertion of an indwelling urethral catheter, has also been studied.

It has virtually been confirmed that the saprophytic organisms of the virgin male urethra are staphylococci, *Str. faecalis,* diphtheroids, *Bact. coli, Str. viridans,* and bacilli of the *Proteus* group.

Recent instrumentation did not appear materially to affect the nature of the urethral bacterial flora.

Presence or absence of organisms in the bladder urine before retention of an indwelling catheter did not appear materially to affect the nature of the bacterial flora which developed subsequent to retention of a catheter.

Before prostatectomy the commonest urethral organism when an indwelling urethral catheter was retained was *Staph. albus.*

After prostatectomy the commonest urethral organism when an indwelling urethral catheter was retained was still *Staph. albus. Bact coli,* however, was almost as common.

The main difference between the bacterial flora of the urethra before and after prostatectomy was the marked development of *Bact. coli* after prostatectomy.

The main difference between the bacterial flora of the bladder urine before and after prostatectomy was the marked development of *Proteus* strains after prostatectomy.

Little relationship was found between the coincidental bacterial flora of the urethra and bladder when an indwelling urethral catheter was retained before prostatectomy. The relationship was closer after prostatectomy, but was by no means complete.

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RESPIRATORY FAILURE IN ACUTE CHEST INFECTIONS

BY

E. KEITH WESTLAKE, M.A., M.D., M.R.C.P.*

Medical Registrar, Department of Medicine, Hammersmith Postgraduate Hospital

Since the introduction of chemotherapy in 1937–8, the mortality in England and Wales from lobar pneumonia among men aged 40–65 has fallen from 500–600 per million to 100 per million. There has, however, been no comparable fall in the death rate from "bronchitis," which has remained at the level of 800–1,000 per million for the last 10 years (Fig. 1). There are at least three possible explanations for this discrepancy: (1) That the majority of patients with "bronchitis" do not receive antibiotic therapy; (2) that the chemical, viral, and bacterial causes of exacerbations of "bronchitis" are not susceptible to the available therapeutic

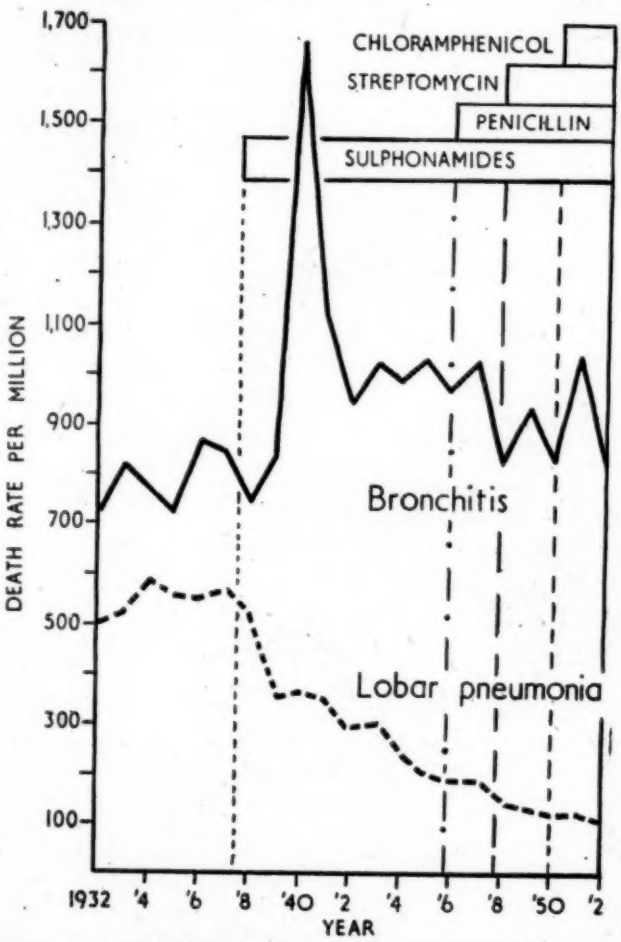

Fig. 1.—Mortality from lobar pneumonia and bronchitis among males aged 40–65 in England and Wales (based on Registrar-General's figures).

*British Medical Association Ernest Hart Memorial Scholar, 1952–3.

agents ; (3) that there are factors additional to infection which influence the prognosis of acute respiratory infections in bronchitic subjects. This paper presents evidence for the third possibility. Bronchitic and emphysematous subjects often manifest an abnormal respiratory response to chest infection, and this may account for the sustained mortality despite the ready availability of penicillin, streptomycin, and chloramphenicol.

Material and Methods

The 30 patients studied included the majority of those with severe respiratory infections admitted to Hammersmith Hospital betwen December, 1953, and April, 1954. Six patients suffering from lobar pneumonia had no previous history of chronic respiratory disease. Twenty-four patients had a long history of chronic bronchitis and were admitted with exacerbations of acute bronchitis, bronchopneumonia, or lobar pneumonia—in 10 of these the respiratory infection had precipitated congestive cardiac failure. On admission a history was taken and a clinical examination made. A sample of arterial blood was obtained by brachial-artery puncture under local analgesia, using a few drops of heparin (5,000 units per ml.) as an anticoagulant. Some patients were too disorientated to give an accurate history, which was then obtained from relatives or from the patient himself on recovery. A sample of sputum was taken for bacteriological examination before starting antibiotic therapy.

Arterial blood was analysed for oxygen content, oxygen capacity, and total plasma carbon dioxide content by the Van Slyke manometric technique (Van Slyke and Neill, 1924). Plasma was obtained under anaerobic conditions by centrifuging blood in capped bijou bottles filled to the brim and transferred immediately to all-glass syringes. The arterial blood *p*H was measured at room temperature within 30 minutes of sampling, using a Cambridge *p*H meter and Stadie closed glass electrode. The meter was standardized with a phosphate-citrate buffer of *p*H 7.40 until a buffer solution of *p*H 7.00 checked within ±0.01 unit. With careful restandardization between each measurement, duplicates agreeing within 0.02 unit could be obtained routinely. Correction of the observed blood *p*H to the patient's body temperature was made by Rosenthal's (1948) factor. Arterial pCO_2 was calculated indirectly from the blood *p*H and total plasma CO_2 content, using a formula derived from the Henderson–Hasselbalch equation.*

On full recovery a further sample of arterial blood was analysed for oxygen saturation, *p*H, and pCO_2 as previously described. The maximum breathing capacity (M.B.C.) was determined using a Siebe-Gorman box valve, collecting expired air through elephant tubing in a Douglas bag, and measuring the volume of gas with a gas meter. This was done both before and after inhalation of a bronchodilator (10 mg. of isoprenaline from a Collison inhaler). This measurement was made in triplicate on at least three occasions before discharge, and subsequently at intervals in out-patients until no further improvement was obtained: this might require a period of observation of three to four months. Repeated measurements of maximum breathing capacity provide as good an assessment of the degree of respiratory impairment in emphysema as any of the more complicated tests of respiratory function.

$$*pCO_2 = \frac{\text{Total plasma carbon dioxide content} \times 14.9}{(\text{antilog } pH - 6.1) + 1}$$

A diagnosis of chronic bronchitis was made in those patients who gave a history of chronic cough and repeated episodes of winter bronchitis ; chronic bronchitis with emphysema if, in addition, a history of dyspnoea on exertion (unrelated to bronchospasm) could be elicited and the M.B.C. was less than 80 litres per minute in males and 60 litres in females. This distinction is purely arbitrary, but post-mortem experience (based on a small personal series) has shown that there is no significant structural emphysema in subjects whose M.B.C.s have previously been recorded as 80 litres or greater. A further diagnosis of cor pulmonale was made if on screening or at necropsy the heart showed right ventricular hypertrophy.

Results

The full results are given in Tables I and II. Fig. 2 depicts the change in oxygen saturation and arterial CO_2 tension between admission and recovery as an oblique arrow. The mean values for arterial oxygen saturation, plasma CO_2 content, pCO_2, and *p*H are given in Table III.

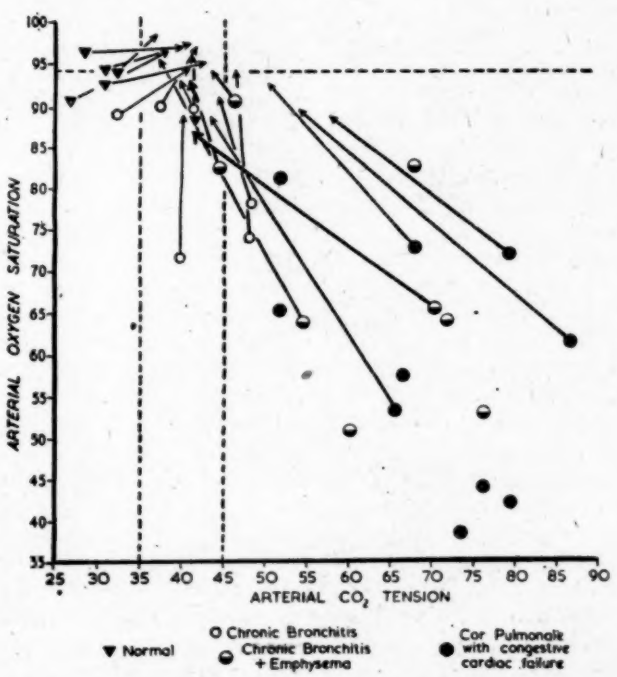

FIG. 2.—Arterial oxygen saturation and carbon dioxide tension on admission with and recovery from an acute respiratory infection. Single points represent patients who died.

The patients studied can be divided into three groups :

(1) *Normal Subjects* (6 cases). The acute respiratory infection was a lobar pneumonia in all subjects. In five the arterial pCO_2 on admission was below normal (less than 35 mm.) with a mild alkalaemia (*p*H 7.43–7.48). Arterial anoxaemia was slight, and in only one case was the oxygen saturation below 90%. In one subject (Case 4) there was no significant change in *p*H or pCO_2. No normal subject had a pCO_2 above normal (higher than 45 mm.) on admission to hospital.

(2) *Bronchitic and Emphysematous Subjects Without Congestive Cardiac Failure* (14 cases).—The acute respiratory infection was a lobar pneumonia in 3, bronchopneumonia in 4, and bronchitis in 7 (this distinction being made on radiological findings). On admission the arterial pCO_2 was below normal in only one patient (Case 18), and above normal (46.2–76.2 mm.) in 9. There was moderate anoxaemia (O_2 saturation 50.8–90.6%), mild to moderate CO_2 retention, and the *p*H was either within normal limits or slightly

TABLE I

No.	Age and Sex	Diagnosis*	Acute Respiratory Infection	Congestive Cardiac Failure	Sputum Bacteriology
1	25 M	Normal chest	Lobar pneumonia	–	*H. influenzae* *Str. pneumoniae*
2	38 F	" "	" "	–	*H. influenzae*
3	44 M	" "	" "	–	*Str. pneumoniae* *H. influenzae*
4	54 M	" "	" "	–	*Str. pneumoniae*
5	58 F	" "	" "	–	*H. influenzae*
6	53 M	" "	" "	–	" "
7	41 M	CB	" "	–	" "
8	72 M	CB, E	Broncho-pneumonia	–	No pathogens
9	67 M	CB, E, HTHD, CP	Bronchitis	–	*Staph. pyogenes*
10	63 M	CB, E	"	–	*H. influenzae*
11	59 F	CB, HTHD	"	–	No pathogens
12	58 F	CB, A, E, CP	"	–	No sputum obtained
13	62 M	CB, E, CP	"	–	*Str. pneumoniae*
14	54 M	CB, E, CP, HTHD	Broncho-pneumonia	–	*H. influenzae* *Str. pneumoniae*
15	58 M	CB, B	"	–	"
16	64 M	CB, E	Bronchitis	–	No pathogens
17	50 M	CB, HT	Broncho-pneumonia	–	" "
18	59 F	CB	Lobar pneumonia	–	*H. influenzae*
19	62 M	CB, E	" "	–	*Str. pneumoniae* *H. influenzae*
20	55 M	CB	Bronchitis	–	*Str. pneumoniae* *H. influenzae*
21	76 M	CB, E, CP	Bronchitis, Broncho-pneumonia	+	" "
22	60 M	CB, E, CP	" "	+	" "
23	54 M	CB, E, CP, HT	" "	+	*Str. pneumoniae* *H. influenzae*
24	44 F	CB, E, CP	" "	+	No sputum obtained
25	67 M	CB, E, CP	" "	+	*Str. pneumoniae*
26	67 F	CB, CP	" "	+	No pathogens
27	70 M	E, CP	Bronchitis	+	*Str. pneumoniae* *H. influenzae*
28	67 M	CB, E, CP	"	+	" "
29	52 M	CB, E, CP	Lobar pneumonia	+	" "
30	64 M	CB, E, CP, HT	Broncho-pneumonia	+	*Str. pneumoniae*

* CB = chronic bronchitis; E = emphysema; A = asthma; CP = cor pulmonale; HT = hypertension; HTHD = hypertensive heart disease; B = bronchiectasis.

TABLE II

	On Admission						On Recovery				
No.	Respiratory Rate	Temperature (°F.)	Oxygen Saturation (%)	*p*H	Plasma CO_2 in Vols. (%)	pCO_2 in mm.	Oxygen Saturation (%)	*p*H	Plasma CO_2 in Vols. %	pCO_2 in mm.	M.B.C. in l. per min. after a Bronchodilator
1	30	102	94·4	7·48	51·4	30·7	97·4	7·40	57·2	40·7	115
2	34	102·6	96·4	7·44	43·3	28·4	97·0	7·42	59·5	40·6	91
3	60	101	92·5	7·46	48·7	30·6	95·2	7·40	59·8	42·5	118
4	32	103	88·9	7·41	59·8	41·7	95·9	7·39	57·1	41·2	96
5	24	103	90·5	7·48	44·8	26·7	97·0	7·44	60·0	38·9	96
6	48	104·6	94·1	7·43	48·4	32·1	98·5	7·44	56·4	36·9	108
7	34	104	89·9	7·44	56·6	37·2	97·0	7·40	58·5	41·6	100
8	40	101·6	65·5	7·32	83·1	70·2	86·9	7·43	61·8	41·2	55
9	26	99·2	82·2	7·31	78·6	67·6	—	—	—	—	—
10	28	99·2	63·9	7·39	75·6	54·5	95·9	7·40	52·6	36·9	51
11	40	101·1	78·4	7·40	67·8	48·3	91·0	7·40	61·7	44·4	—
12	32	100·2	53·1	7·28	82·5	76·2	—	—	—	—	—
13	24	100·8	64·0	7·26	73·8	71·6	—	—	—	—	—
14	36	101·6	50·8	7·36	76·9	60·1	—	—	—	—	—
15	34	103·2	71·5	7·43	64·0	39·8	89·0	7·37	56·4	40·1	42
16	40	98·4	90·6	7·41	65·9	46·2	94·1	7·39	59·5	43·4	47
17	24	100·6	74·4	7·40	67·7	48·1	94·3	7·38	62·2	46·2	93
18	44	100·4	88·9	7·50	56·3	32·1	94·6	7·40	58·0	40·9	66
19	38	101·2	82·6	7·38	60·2	44·4	93·0	7·41	58·8	40·9	58
20	22	100·4	89·6	7·42	60·0	41·2	93·0	7·40	55·7	39·6	81
21	40	99·8	81·4	7·34	64·4	51·7	—	—	—	—	—
22	30	98·2	61·5	7·29	96·5	86·5	89·5	7·41	78·1	53·9	55
23	40	101	73·0	7·34	83·1	67·9	92·6	7·38	67·2	50·2	50
24	30	98·2	44·0	7·22	73·0	76·4	—	—	—	—	—
25	26	100	65·4	7·38	69·5	51·7	—	—	—	—	22
26	25	98·8	38·4	7·25	75·4	73·7	—	—	—	—	—
27	45	98·4	72·3	7·29	87·1	79·2	88·8	7·31	67·2	51·5	53
28	55	97·4	57·5	7·32	79·2	66·5	—	—	—	—	—
29	32	100	53·4	7·33	79·6	65·7	88·8	7·40	61·1	43·4	43
30	30	101	42·1	7·31	90·0	77·5	—	—	—	—	—
Normal Values ..			>94	7·36 –7·44	54–66	35–45				>100 (males) >80 (females)	

low. On recovery, mild anoxaemia persisted in 5 of the 10 survivors, but *p*H and pCO_2 returned to normal limits in all.

(3) *Cor Pulmonale with Congestive Cardiac Failure* (10 cases).—The acute respiratory infection was lobar pneumonia in 1, bronchopneumonia in 7, and bronchitis in 2. Moderate or severe anoxaemia (O_2 saturation 38.4–81.4%), acidaemia (*p*H 7.22–7.38), and hypercapnia (pCO_2 51.7–86.5 mm.) were present in all. Of the 4 survivors mild anoxaemia was present on recovery in all and slight carbon dioxide retention in 3.

A severe degree of anoxaemia and hypercapnia on admission to hospital was associated with a grave prognosis, since of the 10 patients in whom the arterial oxygen saturation was less than 70% and the CO_2 tension higher than 60 mm., only 3 recovered. Fig. 2 graphically illustrates the magnitude of the change in pCO_2 that occurred in some subjects and the fundamentally different respiratory response to pulmonary infection in normal and emphysematous subjects.

Illustrative Case Reports

Case 3. Lobar Pneumonia; Normal Chest.—Man aged 44. Admitted on December 21, 1953, with a week's history of malaise, shivering, and right-sided pleuritic pain. No previous history of cough, dyspnoea, or respiratory illness. Respirations 60 per minute; temperature 101° F. (38.3° C.). Chest radiograph: consolidation of right lower lobe with small pleural effusion. Sputum: *Str. pneumoniae* and *H. influenzae*. Arterial blood: mild anoxaemia with respiratory alkalaemia and hypocapnia. O_2 saturation 92.5%; plasma CO_2 48.7 vols.%; *p*H 7.46; pCO_2 30.6 mm. Treated with penicillin and streptomycin, but developed a massive sterile empyema requiring frequent aspiration. Finally, decortication and resection of the empyema was performed on February 10, 1954. On recovery blood gases had returned to normal (Table II) and the M.B.C. was 118 litres per minute.

Case 8: Chronic Bronchitis, Emphysema, and Bronchopneumonia.—Man aged 72. A 35-years history of chronic cough with mucoid sputum; increasing dyspnoea on exertion for five years; severe attacks of winter bronchitis in 1952 and 1953 following exposure to fog. Admitted on November 10, 1953, with bronchopneumonia: stuporous and unable to give any history; deeply cyanosed. Respirations 40; temperature 101.6° F. (38.7° C.). Too weak to expectorate any sputum. Considerable expiratory bronchospasm. Arterial blood: moderate respiratory acidaemia and hypercapnia; O_2 saturation 65.5%; plasma CO_2 content 83.1 vols.%; *p*H 7.32; pCO_2 70 mm. A chest radiograph showed diffuse coarse mottling; no cardiac enlargement. Treated with penicillin, inhalations of isoprenaline, and continuous oxygen tent. Remained confused, rowdy, aggressive, and uncooperative for a week, but then improved rapidly. On recovery remained chronically anoxaemic (O_2 saturation 86.9%), but *p*H and plasma CO_2 had returned to normal—*p*H 7.43, plasma CO_2 61.8 vols.%, pCO_2 41.2 mm. M.B.C. was reduced to 27 litres, rising to 38 after inhalation of isoprenaline, but gradually increased over succeeding months till in April, 1954, it had become stabilized at 55 litres per minute (after inhalation of isoprenaline).

Case 12: Chronic Bronchitis, Asthma, Emphysema, Cor Pulmonale. Morphine Narcosis.—Woman aged 58. A 30-years history of chronic productive cough, recurrent winter bronchitis, and intermittent attacks of asthma. Previously admitted to Hammersmith Hospital in 1949 moribund, following administration of morphine—comatose, deep cyanosis, jugular venous pressure raised to angle of jaw, respiratory rate 12 per minute—but made an unexpected recovery with oxygen, nikethamide, aminophylline, and penicillin. Investigations in February, 1951, showed right ventricular hypertrophy with mild pulmonary hypertension (pulmonary artery pressure 43/7 mm. Hg); O_2 saturation 84%; mixing curve and subdivisions of lung volumes typical of emphysema. Readmitted on January 6, 1954, with a severe attack of asthmatic bronchitis. Complained of severe throbbing

TABLE III.—*Arterial Blood Gases and pH in Acute Respiratory Infections*

Group	On Admission				On Recovery					Differences between Values on Admission and on Recovery*			
	O_2 Satn. %	Plasma CO_2 Vols.%	*p*H	pCO_2 in mm.	O_2 Satn. %	Plasma CO_2 Vols.%	*p*H	pCO_2 in mm.	M.B.C. l./min.	O_2 Satn.	*p*H	Plasma CO_2 Vols.%	pCO_2 in mm.
1. Normal (Cases 1–6)	92·7	49·4	7·45	31·7	96·8	58·3	7·41	40·1	104	+4·1	+0·04	+8·9	+8·4
2. Chronic bronchitis and emphysema without cardiac failure (Cases 7–20)	74·6	69·1	7·38	51·6	92·9	58·5	7·40	41·5	66	+13·4	+0·01	−7·2	−4·7
3. Cor pulmonale and congestive cardiac failure (Cases 21–30)	54·9	79·8	7·31	69·7	89·9	68·4	7·38	51·0	42	+24·9	−0·07	−18·1	−23·8

* In groups 2 and 3, the differences between admission and recovery are based on surviving patients and not the total number originally studied.

headache and wheeziness. Rational and co-operative despite deep cyanosis. No signs of congestive cardiac failure; blood pressure 145/80; respirations 32; temperature 100.2° F. (37.9° C.). Arterial blood: severe respiratory failure—O_2 saturation 53.1%; plasma CO_2 82.5 vols.%; *p*H 7.28; pCO_2 76.2 mm. Treated with penicillin, oxygen tent, and a mixture of aspirin, phenacetin, and "nepenthe" (containing 8 mg. of morphine). Even this small dose had a disastrous effect, as by the following day the patient was deeply comatose with shallow gasping respirations, rate 15–20; blood pressure 80/60. Arterial O_2 saturation (taken in an oxygen tent) was only 47.8%, and there was a gross respiratory acidaemia—*p*H 6.83 and pCO_2 187 mm. 10 mg. of "nalorphine" was given intravenously, together with nikethamide, aminophylline, and intramuscular cortisone, but respiratory failure had become irreversible, and death occurred eight hours later. There was no necropsy.

Case 13: Chronic Bronchitis, Advanced Emphysema, Cor Pulmonale. Acute Bronchitis; Carbon Dioxide Narcosis.—Man aged 62. A 34-years history of chronic cough with mucoid sputum; increasing dyspnoea on exertion for 7–8 years; recurrent winter bronchitis. Spontaneous tension pneumothorax in December, 1949. Admitted in February, 1954, with a two-weeks history of dyspnoea, wheeziness, increased purulent sputum; visual and auditory hallucinations. On admission: orientated and able to give a reasonable history; moderate pallid cyanosis; diminished air entry over entire chest with expiratory wheeze; respirations 24; temperature 100.8° F. (38.2° C.); no signs of cardiac failure. Chest radiograph: clear lung fields; heart normal size but pulmonary conus prominent. Sputum: profuse growth of *Str. pneumoniae*. Arterial blood: O_2 saturation 64%; *p*H 7.26; plasma CO_2 73.8 vols.%; pCO_2 71.6 mm. Treated with penicillin, streptomycin, and continuous oxygen therapy in a tent. After four hours' oxygen therapy he became semicomatose, with profuse sweating and myoclonic movements of arms—carbon dioxide narcosis had developed: arterial *p*H 7.13 and pCO_2 105 mm. After 24 hours' oxygen therapy, spontaneous improvement occurred and he was conscious though rather confused: the arterial *p*H had returned to 7.26 and the pCO_2 had fallen to 93 mm. Bronchospasm disappeared and the sputum became mucopurulent with a scanty growth of *Bact. coli* only. However, there was no further improvement, and on the seventh day he became semicomatose with a rise in arterial pCO_2 to 121 mm. and a fall in *p*H to 7.12. Donald's (1954) positive-pressure patient-cycled respirator was used in an attempt to increase ventilation, but after 30 minutes the arterial pCO_2 was unchanged and the machine was therefore abandoned. Necropsy: gross structural emphysema of the lungs with bulla formation; mild acute bronchitis with a little mucoid secretion in the trachea and main bronchi; no bronchopneumonia. Heart weight was within normal limits (310 g.), but showed right ventricular hypertrophy (right ventricle 123 g.; left ventricle 113 g.).

Case 14: Chronic Bronchitis, Mild Emphysema, Hypertensive Heart Disease. Bronchopneumonia. Progressive Respiratory Failure.—Man aged 54. Chronic cough with mucoid or mucopurulent sputum for years; intermittent wheeziness; mild dyspnoea on exertion for one to two years; never in bed with chest illness previously. Admitted in March, 1954, with acute bronchitis and bronchopneumonia: mildly disorientated, deep cyanosis; blood pressure 150/95 (230/120 in 1951); presystolic gallop rhythm over ziphisternum but no other signs of cardiac failure; respirations 36; temperature 101.6° F. (38.7° C.). Arterial blood: O_2 saturation 50.8%; *p*H 7.36; plasma CO_2 76.9 vols.%; pCO_2 60.1 mm. Sputum: tenacious and purulent, profuse growth of *H. influenzae* and *Str. pneumoniae*. Treated with penicillin, but no oxygen. Six hours later became restless, stuporous, and finally comatose with deepening cyanosis. Attempts at resuscitation with oxygen, nikethamide, aminophylline, and digoxin proved ineffective. Necropsy: acute tracheobronchitis with gross excess of purulent sputum; chronic bronchitis with generalized dilatation of the smaller bronchi; slight emphysema in the anterior fringes of the lung only; pinhead areas of bronchopneumonic consolidation scattered throughout both lower lobes. Heart enlarged (weight 485 g.), with both left and right ventricular hypertrophy. No coronary atheroma.

Case 22: Chronic Bronchitis, Moderate Emphysema, Cor Pulmonale and Congestive Cardiac Failure. Chloramphenicol Proctocolitis with Terminal Acidaemic Coma.—Man aged 60. "Chesty" all his life; nocturnal wheeziness and increasing dyspnoea on exertion for five years; following exposure to fog in December, 1952, developed a prolonged exacerbation of bronchitis and was admitted to West Middlesex Hospital in May, 1953, in mild congestive cardiac failure. The oedema responded to mersalyl and did not recur until November, 1953. Admitted on November 19, 1953, with a three-weeks history of delusions and nocturnal hallucinations, in moderate congestive cardiac failure and severe respiratory failure; mildly disorientated, euphoric, deeply cyanosed, apyrexial; respirations 40. Arterial blood: O_2 saturation 61.5%; *p*H 7.29; plasma CO_2 96.5 vols.%; pCO_2 86.5 mm. Pulmonary artery systolic pressure moderately raised to 56 mm. Hg. Sputum: scanty growth of *H. influenzae*. Treated with penicillin, streptomycin, digoxin, mersalyl, and oxygen tent for five days. Remained disorientated and hallucinated for a further three weeks, but on discharge on December 20 his mental state had returned to normal, the chest was clear of added sounds, and there was only minimal central cyanosis. The M.B.C. varied between 40 and 55 litres per minute. Sputum was mucoid and grew no pathogens. Arterial blood analysis still showed moderate carbon dioxide retention: O_2 saturation 89.5%; plasma CO_2 78.1 vols.%; *p*H 7.41; pCO_2 53.9 mm. Eight days later he was readmitted with a recurrence of *H. influenzae* bronchitis with profuse purulent sputum and severe bronchospasm. A transient episode of acute respiratory failure with stupor, profuse sweating, coarse myoclonic twitching of the limbs, and rapidly deepening cyanosis was observed on the second day, but this responded to the administration of oxygen and aminophylline. The *H. influenzae* infection was treated with a course of chloramphenicol, but after 24 g. intractable diarrhoea developed and death with severe metabolic acidaemia occurred on the twelfth day (*p*H 7.03; plasma CO_2 38.9 vols.%; pCO_2 61 mm.). Necropsy: chronic bronchitis; mild structural emphysema with small bullae in the upper lobes; a few small areas of bronchopneumonia in the lower lobes; heart enlarged (weight 496 g.) with marked right ventricular hypertrophy (right ventricle 188 g.; left ventricle 172 g.); ulceration of sigmoid colon and rectum.

Case 29 : Chronic Bronchitis, Emphysema, Cor Pulmonale, and Early Congestive Cardiac Failure. Lobar Pneumonia and Carbon Dioxide Narcosis.—Man aged 52. A 16-years history of chronic cough with large quantities of mucopurulent sputum and increasing dyspnoea on exertion. Since pneumonia in 1950 had been unable to work because of dyspnoea. Intermittent oedema of ankles for 18 months. Admitted on January 5, 1954, in early congestive cardiac failure with a confluent left basal bronchopneumonia. Rational and able to give a coherent history despite deep cyanosis. Blood pressure 120/70 ; respirations 32 ; temperature 100° F. (37.8° C.). No gallop rhythm. Arterial blood: O_2 saturation 53.4% ; *p*H 7.33 ; plasma CO_2 79.6 vols.% ; pCO_2 65.7 mm. Treated initially with penicillin and oxygen by "polymask" at 6 litres per minute. After three hours oxygen therapy, lapsed into coma with imperceptible respirations ; hypotension : blood pressure 90/20. A loud presystolic gallop rhythm was audible over the xiphisternum. Arterial blood analysis showed that carbon dioxide narcosis had developed : O_2 saturation 97.5% ; *p*H 7.07 ; pCO_2 102.3 mm. Resuscitated by manual artificial respiration, intravenous nikethamide (15 ml.), aminophylline (0.5 g.) and digoxin (0.5 mg.). Oxygen was temporarily discontinued and three hours later he was again conscious and rational ; the gallop rhythm had disappeared and the blood pressure had risen to 120/55. Oxygen therapy was continued at low rates of flow (2–3 litres per minute) : this was insufficient to relieve his cyanosis completely. Thereafter recovery was slow but uneventful. Mild central cyanosis persisted (O_2 saturation 88.8%), but *p*H and pCO_2 returned to normal (7.40 ; 43.4 mm.). The transverse diameter of the heart shrank by 4 cm. (from 15 to 11 cm.), but screening showed hypertrophy of the right ventricle. He remained incapacitated by dyspnoea, with an M.B.C. fluctuating between 25 and 43 litres per minute.

Discussion

In healthy subjects the sensitivity of the respiratory centre to small change in CO_2 tension provides a delicate homoeostatic mechanism for adjusting pulmonary ventilation to the metabolic needs of the body. The day-to-day variation of pCO_2 during rest, sleep, and moderate activity is probably not more than ± 4 mm. (Mills, 1953). The increased tissue production of carbon dioxide associated with a respiratory infection requires a small increase in pulmonary ventilation to maintain the arterial CO_2 tension at its previous level. However, the combined stimuli of pyrexia, anoxaemia, and the presence of pulmonary consolidation often increase ventilation beyond the level necessary to maintain a normal pCO_2, and the arterial blood CO_2 content may actually be lower than normal (Barach and Woodwell, 1921 ; Hastings *et al.*, 1924 ; Meakins and Davies, 1925 ; Binger *et al.*, 1927). In the six subjects without previous respiratory disease the arterial pCO_2 on admission was either unchanged or lower than the level on recovery (Fig. 2). This may be taken as the normal response to an acute respiratory infection.

By contrast, the physiological response of the chronic bronchitic and emphysematous subject is often grossly abnormal, and the arterial pCO_2 on admission may be up to 32 mm. higher than the patient's habitual level (Fig. 2). Despite the additional stimuli of anoxaemia and pyrexia, the increase in ventilation is insufficient to prevent a rise in the arterial pCO_2 and H-ion concentration. This paradox of hypoventilation in the face of anoxaemia and hypercapnia may be called *respiratory failure*, since it implies a breakdown of the homoeostatic function of the respiratory centre in maintaining the arterial CO_2 tension and H-ion concentration within normal limits. On this definition many emphysematous subjects are in chronic respiratory failure even when free from intercurrent respiratory infection (Scott, 1920 ; Baldwin *et al.*, 1949), since their arterial CO_2 tensions are permanently raised above 45 mm. However, a chest infection will frequently precipitate acute respiratory failure in subjects whose CO_2 tensions are within normal limits when well. This occurred in 10 of the 24 bronchitic subjects studied. It should be noted that it is unnecessary to measure pCO_2 to detect the presence of respiratory failure. Unless there are grounds for suspecting concomitant metabolic alkalaemia, a total plasma carbon dioxide content of arterial blood raised above 66 volumes indicates respiratory failure (Table II).

In general, a respiratory infection in the emphysematous subject is associated with a more severe degree of anoxaemia than in a normal subject. In a study of 130 cases of lobar pneumonia, Binger (1928–9) found that the oxygen saturation was above 70% in 104 (80%) ; by contrast, 12 of the 24 bronchitic subjects in this study had saturations less than 70%. There are two reasons for this.

Firstly, many emphysematous subjects are chronically anoxic. Imbalance between alveolar perfusion and ventilation may reduce the arterial oxygen tension (pO_2) to 50–80 mm. (normally 90–100). With the development of a respiratory infection, alveolar perfusion–ventilation ratios may become even more abnormal, and the arterial oxygen saturation rapidly falls to seriously low levels with the appearance of deep cyanosis and mental confusion.

Secondly, respiratory failure with rising carbon dioxide tensions is inevitably associated with arterial anoxaemia. The interrelationship between alveolar oxygen and carbon dioxide tensions can best be appreciated by consideration of the equation derived by Fenn, Rahn, and Otis (1946).* When the barometric pressure is 760 mm. and the respiratory quotient (RQ) is 0.79, this simplifies to alveolar $pO_2 = 150 - 1.21 \times$ alveolar pCO_2. If the alveolar pCO_2 rises to 70 mm. the alveolar pO_2 must fall to 65 mm.—and the arterial pO_2 cannot, of course, be higher than this. The severe degrees of anoxaemia found in emphysematous subjects during acute respiratory infections are therefore due to a combination of respiratory failure—causing hypoventilation and a low alveolar oxygen tension—and the direct effect of pulmonary infection increasing an already large alveolar-arterial pO_2 gradient : in many instances the former is quantitatively more important than the latter.

The Mechanism of Respiratory Failure

It may be physically impossible to maintain adequate pulmonary ventilation when the maximum ventilatory capacity is grossly diminished. In severe status asthmaticus intense bronchospasm may reduce the ventilatory capacity *below* the normal level of resting ventilation : under these circumstances anoxaemia and carbon dioxide retention must rapidly occur. However, most patients in respiratory failure have a small breathing reserve. I have often been able to demonstrate at the bedside that a considerable increase in ventilation occurs when these patients are commanded to breathe more slowly and deeply. When the extra cortical stimulus to respiration is withdrawn they rapidly revert to ineffective shallow gasps. In these patients the respiratory centre must have become insensitive to the stimuli of anoxaemia, hypercapnia, H-ion concentration, and pyrexia. It is well known that the respiratory response to carbon dioxide is considerably diminished in emphysema (Scott, 1920), and Prime and Westlake (1954) have shown that the response diminishes with rising levels of resting arterial pCO_2. At a resting carbon dioxide tension of 65–70 mm. the respiratory response is only 10–20% of normal. Anoxia may be an important factor precipitating respiratory failure, since Newburgh *et al.* (1916) and Ivy *et al.* (1947) have shown that severe anoxia depresses the sensitivity of the respiratory centre to carbon dioxide. Thus respiratory failure may become a rapidly progressive process (cf. Case 14) ; for, as Drinker (1945) has shown, low oxygen tensions cause pulmonary oedema with consequent further increase of anoxaemia.

*Mean alveolar $pO_2 = (\text{Barometric pressure} - 47) \times 0.21 - \text{alveolar } pCO_2 \left(0.21 + \frac{0.79}{RQ}\right)$

The Clinical Picture of Respiratory Failure

Acute respiratory failure is responsible for the distinctive clinical features observed during exacerbations of respiratory infection in bronchitic subjects. Anoxaemia, acidaemia, and hypercapnia give rise to cerebral vasodilatation and increased cerebral blood flow, which in turn raises C.S.F. pressure and causes papilloedema and headache (Patterson *et al.*, 1952; Westlake and Kaye, 1954). They also result in increased cardiac output with warm extremities and increased pulse pressure (McMichael and Sharpey-Schafer, 1944), impaired cerebral function with disorientation, restlessness, hallucinations, delusions, myoclonic twitching, and profuse sweating. It is well known that cardiac failure in pulmonary heart disease is always associated with anoxaemia and high levels of blood carbon dioxide (Peters, Bulger, and Eisenman, 1925; Taquini *et al.*, 1948). In the 14 patients studied by Platts (1953) the oxygen saturation was below 72% and the CO_2 content of whole arterial blood higher than 56 volumes in all but one. In this study moderate or severe anoxaemia, acidaemia, and hypercapnia were present in all ten patients with congestive failure. These observations suggest that congestive cardiac failure in pulmonary heart disease is secondary to respiratory failure. The exact mechanism involved is not fully elucidated, but there is no doubt that anoxaemia raises the pulmonary artery pressure by direct vasoconstrictor action on the pulmonary arterioles (Motley *et al.*, 1947); high carbon dioxide tensions have a similar effect (von Euler and Liljestrand, 1946; Yu *et al.*, 1953). Lange *et al.* (1951) have shown that acidaemia causes a considerable increase in cardiac output and fall in peripheral resistance. In the final stages, respiratory failure causes cardiovascular collapse with coma, falling cardiac output, peripheral vasoconstriction, hypotension, pulmonary oedema, diminished renal blood flow, and elevated blood urea levels.

The Treatment of Respiratory Failure

Treatment is based on: (1) antibacterial treatment to counter the pulmonary infection; (2) oxygen therapy to relieve anoxaemia; (3) relief of respiratory obstruction by the use of antispasmodics, postural drainage and coughing. *H. influenzae* is an important pathogen in exacerbations of respiratory infection in the chronic bronchitic (Mulder *et al.*, 1952; May, 1953; Elmes, Knox, and Fletcher, 1953), and was isolated from the sputum in 12 of my 24 bronchitic subjects. The predominance of this organism suggests that the initial treatment (prior to obtaining a full bacteriological report) should be one capable of eradicating *H. influenzae*. Streptomycin and chloramphenicol in doses of 1 g. six-hourly are effective, whereas crystalline penicillin in usual doses is not. However, massive doses of one of the penicillin esters—for example, "estopen," 1 mega unit b.d.—may raise the concentration of penicillin in the sputum to inhibitory levels. Apart from the minor risk of subsequent aplastic anaemia, chloramphenicol has one disadvantage: the intractable diarrhoea that occasionally follows its use may tip the scales against recovery in a gravely ill patient (cf. Case 12 and two others not included in this series).

In the severely anoxic patient oxygen therapy is essential to prevent sudden cardiovascular collapse or death from progressive respiratory failure. It is not, however, without dangers of its own. In respiratory failure, ventilation is principally maintained by the reflex drive of anoxia stimullating the carotid and aortic chemoreceptors. Relief of anoxia abolishes this drive and ventilation falls, with consequent further rise in the arterial CO_2 content. Eventually a new respiratory equilibrium is reached when the higher level of arterial pCO_2 and H-ion compensates for the absent anoxic stimulus (Westlake, 1953). The rise in carbon dioxide content may be sufficient to cause carbon dioxide narcosis with mental confusion, twitching, headache, sweating, stupor, and coma (cf. Cases 13 and 29). Severe carbon dioxide narcosis can often be prevented by giving oxygen at low rates of flow so that anoxaemia is only partially relieved and the consequent rise in blood carbon dioxide is too small to cause adverse symptoms. Oxygen via a B.L.B. mask or the lightweight "polymask" (B.O.C.) at 1–3 litres per minute is a satisfactory technique (Barach, 1948; Simpson, 1954). An oxygen tent cannot be used, since with low rates of flow of oxygen the internal temperature rises too high.

Patients with respiratory failure are often given morphine on the erroneous assumption that they are suffering from pulmonary oedema. This mistake may prove rapidly fatal by abolishing the residual sensitivity to carbon dioxide, but, fortunately, the depressant effect of morphine can be immediately reversed by an injection of n-allyl normorphine ("nalorphine," "lethidrone"), but this must be administered before respiratory failure has progressed to an irreversible stage (cf. Case 12). Nalorphine is of no value in reversing spontaneous respiratory failure or that due to barbiturate overdosage. Bronchospasm will usually respond to standard therapeutic measures, but in resistant cases A.C.T.H. or cortisone may avert a fatal outcome. Cortisone appeared to be life-saving in Case 10, but A.C.T.H. was given too late in Case 21. The importance of clearing the bronchial tree of secretions cannot be overemphasized. Patients in respiratory failure are often too weak or apathetic to cough up their sputum spontaneously. They should be encouraged to cough at regular intervals (every one to two hours) by the nursing staff, but if this fails to raise the sputum the rapid intravenous injection of 3–4 ml. of nikethamide accompanied by vigorous thumping on the chest may be effective (Elmes, personal communication, 1954).

A direct method of treating respiratory failure (by increasing ventilation mechanically)—of proved effectiveness and general applicability—is not yet available. Callaway and McKusick (1951) have reported favourably on the use of a pneumoperitoneum, and Boutourline-Young and Whittenberger (1951), Stone *et al.* (1953), and Lovejoy *et al.* (1954) have claimed successes with mechanical ventilation in a Drinker tank respirator. In my own experience, the Paul–Bragg pulsator, the Drinker tank respirator (Westlake, 1953), and Donald's positive-pressure patient-cycled respirator (cf. Case 13) have all proved ineffective in increasing the ventilation of patients in severe respiratory failure.

Conclusion

The importance of respiratory failure lies in the frequency with which it proves fatal before therapeutic measures have had time to cure the causal pulmonary disease. It is well known that many deaths occurred within a few hours of exposure to the dense fog of December, 1952 (Logan, 1953). Further advances will depend on the discovery of effective methods of maintaining or increasing ventilation in bronchitic subjects. In many cases, however, we are dealing with an irrevocably damaged lung and can do little more than postpone death for a few years. It is unlikely that there will be any substantial fall in the overall mortality from "bronchitis" until the incidence of chronic bronchitis and emphysema is itself reduced. This will depend on the discovery of all the aetiological factors involved. Overcrowding, excessive smoking, and atmospheric smoke pollution are probably important, but their correction will involve forms of social therapy which are, unfortunately, not within the direct grasp of the medical profession.

Summary

Arterial blood gases and *p*H have been studied in 30 patients admitted to hospital with an acute respiratory infection: in 6 subjects without previous history of chest disease the arterial CO_2 tension was unchanged or was lower than the level on recovery. This is the normal physiological response to respiratory infection.

In 18 of the 24 subjects with bronchitis or emphysema the response was abnormal and the initial arterial CO_2 tension was 5–32 mm. higher than on recovery. These patients may be said to have been in respiratory failure on admission to hospital.

Acute respiratory failure with increasing anoxaemia, hypercapnia, and acidaemia is responsible for the distinctive clinical picture observed during exacerbation of infection in the chronic bronchitic and emphysematous subject: headache, raised intracranial pressure, papilloedema, mental confusion, hallucinations, sweating, myoclonic jerking, increased cardiac output, pulmonary hypertension, and congestive cardiac failure.

Mortality from "bronchitis" has not declined in the last 10 years despite antibiotic therapy: respiratory failure may be a partial explanation of this phenomenon.

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In 1950 Dr. Erik Waller, of Stockholm, presented his library to the University of Upsala (see *Journal*, December 23, 1950, p. 1452). This library comprises about 21,000 items, principally concerned with the history of medicine and science. More than twice the size of Osler's library at McGill, it is one of the most valuable collections of its kind in the world, and represents the result of scholarly collection over a period of forty years. It includes 150 books printed before 1500, a hundred editions of Vesalius (including a unique copy of an edition of the *Epitome*), fifty editions of Harvey, forty-three of Paré, and a large collection of Linneana. Almost all the great names in medicine are represented; there are also many works on the history of medicine. The catalogue of the Bibliotheca Walleriana has now been compiled (in English) by the university librarian of Upsala and is to be published early next year by Messrs. Almqvist and Wiksell, Stockholm, at a subscription price of 175 Swedish kronor (200 kr. after December 31).

THE FACTOR OF INFECTION IN HEART FAILURE

BY

F. J. FLINT, M.A., D.M., M.R.C.P.

Physician to the City General Hospital, Fir Vale Infirmary, and Nether Edge Hospital, Sheffield

"A neglected cold is frequently the original cause of the most severe diseases of the heart."—Laennec, 1834.

This review of 300 patients suffering from congestive heart failure (159 males and 141 females) who were admitted consecutively to the City General Hospital, Sheffield, between March 17, 1952, and March 16, 1953, is designed to call attention to the high incidence of respiratory infections in heart failure and to demonstrate their importance as the commonest precipitating cause of heart failure, even in patients with intrinsic heart disease.

In this survey a diagnosis of congestive heart failure demanded an unequivocal rise of cervical venous pressure above the sternal angle during all phases of respiration, and either peripheral oedema or hepatic engorgement. In most cases all three signs were present.

Each patient was examined by me for the purpose of this investigation and a full clinical history was recorded on a standard "pro-forma" which paid particular attention to respiratory symptoms. Routine investigation comprised an electrocardiogram, an *x*-ray film and screening of the chest, leucocyte count, examination of the urine and sputum, and estimation of the haemoglobin and Wassermann and Kahn reactions.

Clinical Material

Cases having more than one cause are classified under the heading of the major lesion, except for 12 cases of cor pulmonale in which the pulmonary lesion was thought to be predominant, but which are classified under the heading of the associated cardiac lesion and designated "associated cor pulmonale."

1. *Cor Pulmonale.*—Total, 76 (64 males, 12 females); 26 deaths; 24 necropsies. All these patients had severe lung disease, manifested central cyanosis, and had sinus rhythm. None showed evidence of hypertensive, ischaemic, rheumatic, or other intrinsic heart disease.

Chronic bronchitis	42 cases
Bronchiectasis	21 ,,
Asthma	5 ,,
Pneumoconiosis	5 ,,
Severe kyphoscoliosis	2 ,,
Organizing pneumonia	1 case

2. *Rheumatic and Non-specific Valvular Lesions.*—Total 68 (26 males, 42 females); 18 deaths; 14 necropsies.

Isolated mitral valve disease	38 cases
Isolated aortic valve disease	9 ,,
Combined aortic and mitral valve disease	21 ,,
Associated cor pulmonale	3 ,,

3. *Ischaemic Heart Disease.*—Total, 65 (33 males, 32 females); 34 deaths, 23 necropsies.

Recent myocardial infarction	26 cases
Old myocardial infarction	28 ,,
Infarction not proved (angina in all)	11 ,,
Associated hypertensive heart disease	7 ,,
Associated aortic stenosis	1 case
Associated cor pulmonale	4 cases

4. *Hypertensive Heart Disease.*—Total, 63 (26 males, 37 females); 24 deaths; 20 necropsies.

"Primary hypertension"	49 cases
Chronic nephritis with uraemia	11 ,,
Acute nephritis	3 ,,
Associated cor pulmonale	4 ,,

5. *Miscellaneous Group:* (*a*) *Syphilis.*—Total, 6 (5 males, 1 female); 2 deaths; 2 necropsies.

Aortitis with aortic incompetence (W.R. pos.)	5 cases
Aortic aneurysm	1 case
Associated cor pulmonale	1 „

(*b*) *Severe Anaemia.*—Total, 9 (2 males, 7 females); no death. (Hb 30%–50%, 2 cases; Hb <30%, 7 cases.)

Pernicious anaemia	6 cases
Iron deficiency anaemia	1 case
Myelomatosis	1 „
Carcinomatosis (breast)	1 „

(*c*) *Thyrotoxicosis.*—Total, 2 (both females); no death.

(*d*) *Severe Liver Disease.*—Total, 4 (2 males, 2 females); 3 deaths; 2 necropsies.

Hepatic cirrhosis	2 cases
Metastatic carcinoma	2 „

(*e*) *Congenital Heart Disease.*—Total, 2 (females); 1 death; 1 necropsy.

Atrial septal defect	1 case
Patent ductus arteriosus	1 „

(*f*) *Aetiology Uncertain.*—Total, 5 (1 male, 4 females); 3 deaths; 2 necropsies.

Seasonal Incidence of Heart Failure

The seasonal incidence of admissions in this series is described in Figs. 1–5. There were also two cases with pulmonary tuberculosis, which is not listed in the diagrams as a respiratory infection.

Cor pulmonale was less common in the summer, only 17 cases being admitted during the months of May to October, but 59 cases from November to April. In the other groups, with the exception of the miscellaneous cases, the incidence of admissions was about twice as high in the winter as in the summer, suggesting that this was due to the prevalence of respiratory infections during the winter months.

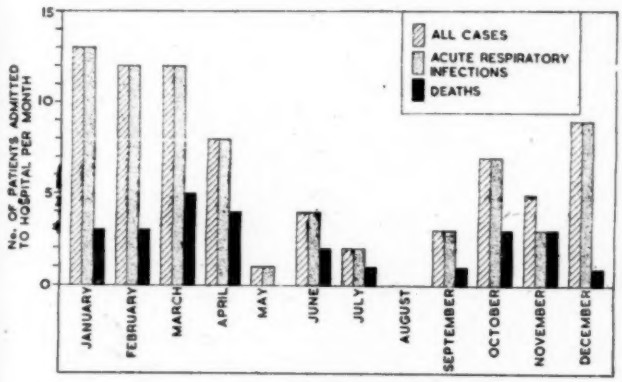

FIG. 1.—Incidence of cor pulmonale. May–October: 17 cases—acute respiratory infections 17; deaths 7. November–April: 59 cases—acute respiratory infections 57; deaths 19.

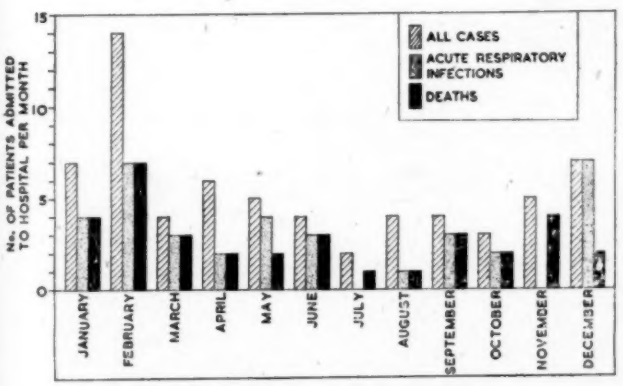

FIG. 2.—Incidence of ischaemic heart disease. May–October: 22 cases—acute respiratory infections 13; deaths 12. November–April: 43 cases—acute respiratory infections 23; deaths 22.

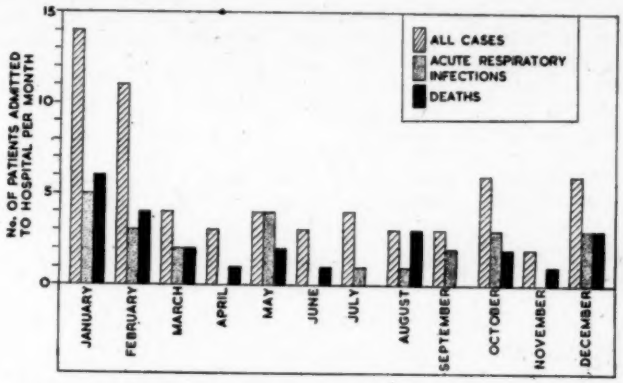

FIG. 3.—Incidence of hypertensive heart disease. May–October: 23 cases—acute respiratory infections 11; deaths 8. November–April: 40 cases—acute respiratory infections 14; deaths 16.

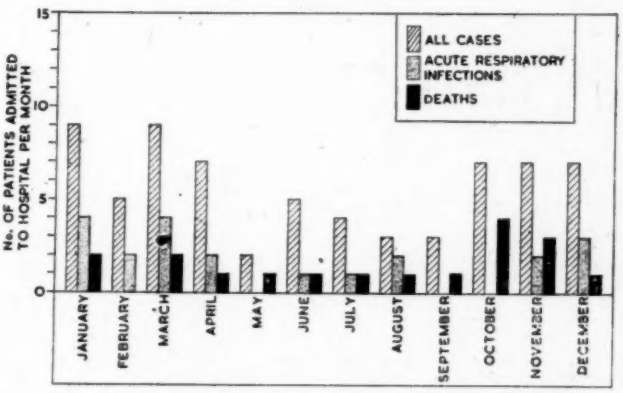

FIG. 4.—Incidence of rheumatic heart disease. May–October: 24 cases—acute respiratory infections 4; deaths 9. November–April: 44 cases—acute respiratory infections 17; deaths 9.

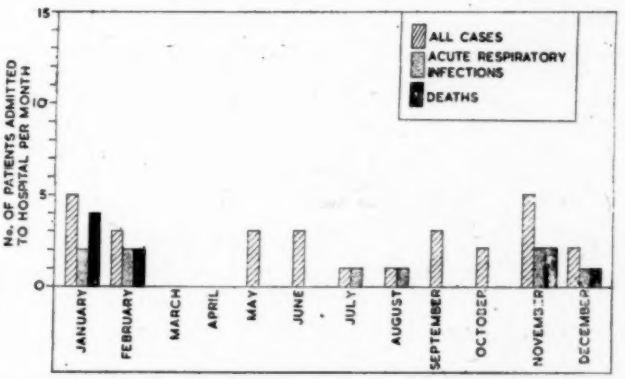

FIG. 5.—Miscellaneous group: severe anaemia, thyrotoxicosis, syphilis, congenital heart disease, severe liver disease, and others. May–October: 13 cases—acute respiratory infections 2; deaths 0. November–April: 15 cases—acute respiratory infections 7; deaths 9.

Incidence of Respiratory Infections and of Other Precipitating Causes of Heart Failure

Of 300 cases in all groups, 167 showed evidence of bronchitis, pneumonia, or other respiratory infection. In 156 of these cases heart failure was immediately preceded by the infection which was present on admission to hospital and which usually began as a cold or influenza (Table I). In the remaining 11 the respiratory infection was usually of the aspiration type, occurring in patients who were comatose or semicomatose from cerebral vascular thrombotic lesions or uraemia. It is suggested that in the majority

of cases a respiratory infection was not merely a secondary or terminal factor but the immediate cause of heart failure because the first symptoms—coryza, sore throat, or cough with purulent sputum—were attributable to respiratory infection rather than to heart failure. Table I describes the incidence and nature of the primary infections occurring in the different groups, but does not include those infections which were believed to be secondary; it also summarizes the other causes of heart failure.

TABLE I.—*Precipitating Causes of Heart Failure—All Groups: 159 Males; 141 Females*

	Ischaemic Heart Disease	Hypertensive Heart Disease	Rheumatic Heart Disease	Miscellaneous Group	Cor Pulmonale	All Groups Combined
I. Diseases of the heart						
Recent myocardial infarction	25	—	—	—	—	25
Active rheumatic carditis	1	1	1	—	—	3
Bacterial endocarditis	—	—	3	—	—	3
II. Diseases of the lungs						
Acute bronchitis	14	16	14	5	54†	103
Pneumonia:						
All cases	15	7	6	3	20	51
Lobar, segmental	10	4	3	1	2	20
Bronchopneumonia	4	2	2	2	13	23
Lung abscess*	1	1	1	—	3	6
Empyema	—	—	—	—	1	1
Organized pneumonia	—	—	—	—	1	1
Tuberculosis	—	—	2	—	—	2
Pulmonary embolism	2	2	7	—	—	11
III. Factors causing hypervolaemia						
Anaemia:						
Chronic anaemia	—	—	1	9	—	10
Massive haemorrhage from gastric or duodenal ulcer	—	—	4	—	—	4
Sodium and water retention:						
Acute nephritis	—	3	—	—	—	3
Chronic nephritis—uraemia	—	9	—	—	—	9
Prostatic hypertrophy (urinary retention)	1	2	—	—	—	3
Insulin	1	1	—	—	—	2
IV. Cardiac tamponade						
Pericardial effusion	—	—	1	—	—	1
V. Miscellaneous						
Cerebral thrombosis—hemiplegia	—	3	—	—	—	3
Paroxysmal auricular fibrillation	—	1	2	—	—	3
Myxoedema	—	1	—	—	—	1
VI. Precipitating cause not elicited	6	17	27	11	2	63
Total No. of Patients	65	63	68	28	76	300

* Five patients with lung abscess also had bronchial carcinoma.
† One patient with bronchitis also had a tension pneumothorax.

Table I shows that respiratory infections precipitated heart failure in 74 of the 76 patients with cor pulmonale: bronchitis in 54, bronchopneumonia in 13, lobar or segmental pneumonia in 2, lung abscess or empyema in 4, and an unusual form of diffuse organizing pneumonia in the other. Bronchial infections in this group were thus predominant, and cultivation of the sputum yielded a mixed growth of organisms: of 42 cases whose sputum was thoroughly examined, including mouse inoculation, pneumococci were isolated from 30 and *Haemophilus influenzae* from 10.

In the 224 cases of heart failure not due to cor pulmonale, respiratory infections precipitated heart failure in 82: bronchitis in 49, lobar pneumonia in 18, bronchopneumonia in 10, and lung abscess in 3. Two patients had pulmonary tuberculosis, in one as a pleural effusion, in the other as a spreading parenchymal lesion. The signs of pneumonic consolidation were often masked by the heart failure. Pyrexia was often absent because of peripheral circulatory failure. In many cases bronchitis was detected only if care was taken to inspect the sputum. Unilateral chest dullness was more often due either to a pneumonia or to an effusion secondary to pulmonary infarction than to a simple hydrothorax. Tubular breathing was sometimes absent, probably because of bronchial occlusion by pus or oedema fluid.

There were 144 patients in whom there was no evidence that heart failure had been precipitated by bronchitis or pneumonia. Precipitating causes of the heart failure, which are summarized in Table I, were elicited in 81 of these, and in many of the remaining 63 cases it was thought that heart failure had been precipitated by a cold or influenza.

Considering the 156 patients with precipitating respiratory infections, 11 of the 18 who were over 70 years of age died, compared with 42 of the remaining 138 (Table II). Respiratory infections were thus particularly lethal in patients

TABLE II.—*The Age Distribution and Mortality Rate of Patients Whose Heart Failure was Precipitated by Bronchitis or Pneumonia*

Aetiology	Cases under 70		Cases over 70	
	All Cases	Deaths	All Cases	Deaths
Ischaemic heart disease	18	4	11	8
Hypertensive heart disease	19	5	4	2
Rheumatic heart disease	22	6	—	—
Miscellaneous group	8	4	—	—
Cor pulmonale	71	23	3	1
All groups	138	42	18	11

over 70, especially those with ischaemic heart disease, but the high recovery rate in those under 70 demonstrates that these infections are by no means to be regarded as terminal events.

Causes of Death

Heart failure disturbs the functioning of all organs of the body, so it is often difficult to assess the precise cause of death. In many cases, however, the objective signs of congestive failure such as peripheral oedema, pulmonary oedema, and raised venous pressure have disappeared before death, which may be due to some complicating factor.

117 patients died—111 during their first admission to hospital and 6 during a subsequent admission. Table III

TABLE III.—*The Causes of Death Elicited at Necropsy in Cases of Heart Failure: 88 Cases*

	Ischaemic Heart Disease	Hypertensive Heart Disease	Rheumatic Heart Disease	Miscellaneous Group	Cor Pulmonale	All Groups
No. of cases: Total	65	63	68	28	76	300
" " " Deaths during first admission	34	24	18	9	26	111
No. of cases: Deaths during subsequent admission	3	—	2	—	1	6
No. of cases: Necropsies	23	20	14	7	24	88
Causes of death						
I. Respiratory infections: Total	7	5	2	2	22	38
Pneumonia:						
All cases	6	4	1	1	9	21
Lobar, segmental	3	2*	—	—	—	5
Bronchopneumonia	2	2	1	1	7	13
Abscess	1	—	—	—	—	1
Empyema	—	—	—	—	1	1
Organized pneumonia	—	—	—	—	1	1
Acute bronchitis with respiratory insufficiency	1†	1†	1†	1	13	17
II. Other causes:						
Cardiac failure with pulmonary oedema	9	2	5	1	—	17
Rupture of the heart	2	—	—	—	—	2
Obstruction of mitral valve by left auricular thrombus	—	—	2	—	—	2
Tension pneumothorax	—	—	—	1	—	1
Pulmonary embolism	3	2	3	—	—	8
Uraemia	—	9	—	—	—	9
Massive gastro-intestinal haemorrhage	2	—	—	—	2	4
Cerebral: haemorrhage, embolism, thrombosis	—	2	1	—	—	3
Bacterial endocarditis	—	—	1‡	—	—	1
Liver failure	—	—	—	1	—	1
Carcinomatosis	—	—	—	1	—	1
Uncertain	—	—	—	1	—	1

* One of these two patients also had intestinal obstruction, the other diabetic ketosis.
† Pneumoconiosis.
‡ This patient died from acute pancreatitis due to bacterial embolism.

gives the principal cause of death in 88 of the 117 patients on whom post-mortem examination was permitted. Permission for examination was granted in only 11 of the 23 patients over 70. Death occurred within 48 hours of admission to hospital in only 23, nine of whom had coronary thrombosis.

Uncomplicated heart failure was the cause of death in only 17 of the 88 cases. In 21 cases death was due to pneumonia which had precipitated heart failure. Pneumonia of the secondary or hypostatic type occurred only if the patient had been in coma or semicoma; it was revealed in several patients who had been unconscious because of a cerebral vascular accident or uraemia.

There is good reason to believe that in nearly all cases of cor pulmonale, and in at least 16 of the 64 cases in other groups, death was directly attributable to a respiratory infection which itself had been the immediate cause of heart failure.

Discussion

It has long been accepted that congestive cardiac failure in cases of cor pulmonale is precipitated by a respiratory infection. In persons with grossly diminished functioning lung tissue the asphyxiating process induced by respiratory infections is thought to give rise to pulmonary hypertension, sodium and water retention, and, subsequently, failure of the right heart (Harvey *et al.*, 1951; Mounsey *et al.*, 1952; Donald, 1953). In patients with congestive heart failure due to ischaemic heart disease, hypertensive heart disease, rheumatism and other causes, however, hypoxia and hypercapnia are only slight in degree compared with the gaseous disturbance in cor pulmonale (Platts, 1953), so that another explanation must be sought for the mechanism whereby in those other forms of heart disease congestive heart failure is often precipitated by a respiratory infection.

There are at least two possible explanations. First, in the case of patients suffering from either left heart failure or mitral stenosis, the resulting pulmonary congestion causes pulmonary oedema, which is an excellent medium for the growth of bacteria even of low virulence. Thus patients with commencing pulmonary congestion are particularly susceptible to bronchitis or pneumonia during the course of a cold or influenza; and this infection, by potentiating the development of oedema fluid, may increase the pulmonary resistance to right ventricular output and lead to overloading.

The second possibility is that the infection may, directly or indirectly, damage the myocardium. There is no doubt that, in common with other infections, pneumonia can cause myocarditis, which, especially in persons with pre-existing heart disease, may lead to cardiac failure. Saphir (1941, 1942), in analysing the cause of myocarditis in 240 cases at necropsy, considered that 19 were accounted for by bronchopneumonia and 7 by lobar pneumonia. Saphir and Amromin (1948), in a study of the hearts at post-mortem examination of 67 patients who had died of pneumonia, found histological evidence of myocarditis in 26 (38.8%), in that the heart muscle was flabby, the ventricles were dilated, the myocardium contained haemorrhages and in some presented a tigroid appearance, and there were petechial haemorrhages in the pericardium. Histologically, in every instance there were inflammatory cells with exudate in the interstitial tissues, and scattered areas of degeneration of muscle fibres. These changes were scattered throughout the heart and would sometimes have been missed if serial sections had not been taken.

Electrocardiograms taken during and immediately after severe pneumonia may show various arrhythmias, low voltage, and sometimes important changes such as all grades of heart block and inversion of the T wave in standard lead I or in the left ventricular chest leads (Wood, 1950). Thomson *et al.* (1946) observed flattening or depression of the T wave in 35 (43%) of 82 cases of pneumonia, which in 23 cases was reversible. It is likely that in patients with pre-existing coronary artery disease the T-wave changes, which are similar to those described by Wood and his colleagues (1950) as occurring on exercise, are induced by acute coronary insufficiency.

The most marked circulatory disturbance in pneumonia and other severe infections is peripheral circulatory failure due either to paralysis of the nerve centres or to paralysis of the smaller arterioles and capillaries. The state of shock resulting in a fall of blood pressure may further embarrass the circulation by reducing the coronary blood supply.

Myocarditis in pneumonia is unlikely to be a common cause of congestive heart failure. More frequent perhaps than is usually supposed, it is, however, most likely to occur in the fulminant form of pneumonia before there has been time for congestive heart failure to develop. Bronchitis, which is rarely associated with bacteriaemia, is unlikely to produce myocarditis. The relatively high incidence of bronchitis as an accompaniment of heart failure in patients with non-pulmonary heart disease (49 of 244 cases in the present series) suggests that respiratory infections embarrass the circulation by some mechanism which has not yet been elucidated.

Conclusion

The present series illustrates both the necessity and the difficulty of arriving at a complete diagnosis, which should include the precipitating cause of failure as well as the basic cardiac lesion. Analysis of the present series (Table I) clearly shows how diverse and complex are these factors. Bronchitis and pneumonia were together responsible for failure in half the cases and for death in two-fifths. Owing to the prevalence of respiratory infections in industrial areas, it is unlikely, however, that the figures are applicable to the country as a whole.

The clinical manifestations of respiratory infections tend to be masked by heart failure, and the possibility of infection must be continuously borne in mind. In a patient with heart disease, bronchitis is likely to be serious; therefore, examination is not complete without inspection of the sputum.

In many cases of heart failure, particularly those occurring in the winter, chemotherapy is probably more important than any other single item of treatment, more important even than digitalis or mersalyl. Further work is in progress to discover which antibiotic is the most useful for the treatment of bronchitis, but for most forms of pneumonia the drug of choice initially is penicillin (M.R.C. Report, 1951; Flint, 1953).

Summary

From a study of 300 cases of heart failure in an industrial city, it was found that over half (167 cases) had some form of respiratory infection. In 156 cases there was good evidence that the respiratory infection was the precipitating cause of failure (bronchitis in 103, pneumonia in 51, tuberculosis in 2), and in only 11 patients, most of whom were comatose, was it thought to be secondary.

Heart failure was precipitated by a respiratory infection in 74 of the 76 patients with cor pulmonale and in 82 of the remaining 224 patients with other forms of heart disease. The incidence of heart failure in winter was twice that in summer.

Post-mortem examination was performed in 88 cases. Death was due to pneumonia in 21 cases and to acute bronchitis in a further 17.

The mechanism whereby acute respiratory infections give rise to heart failure is discussed.

It is suggested that antibiotics are at least as important as either digitalis or mersalyl in the treatment of heart failure.

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INSULIN RESISTANCE

BY

DOUGLAS HUBBLE, M.D., F.R.C.P.

Physician, Derbyshire Royal Infirmary, Derby City Hospital, and Derbyshire Hospital for Sick Children

Insulin resistance in diabetics is usually defined as a state in which more than 200 units of insulin daily are required to lower the blood sugar to normal levels, such resistance being maintained for not less than 48 hours. This definition, although arbitrary, may be usefully retained until the nature of insulin resistance is understood. It is well recognized that infection and ketosis increase insulin requirements and that insulin resistance is present in some patients in diabetic coma, though whether the involved mechanisms are related to the insulin resistance which occurs in the absence of these states is quite unknown.

It is also recognized that the young insulin-sensitive diabetic oscillates rapidly from hypoglycaemia to hyperglycaemia and ketosis, even under controlled conditions in hospital, and in the absence of infection or other relevant environmental disturbance. In such children there is also a notable disposition to nocturnal hyperglycaemia. Payne (1953) has found that this instability of insulin control is not uncommon in diabetic girls at puberty, and that it can sometimes be avoided by a small dose of oestrogen given in the premenstrual phase.

Smelo in 1948 reviewed 54 cases of insulin resistance in the English literature to that time. Only two of these cases occurred in children. For the entire series of 54 cases, Smelo records a death rate of 41%. He regards the prognosis of the condition as relatively benign, however, and suggests that more careful control and the use of larger doses of insulin would achieve more successful results.

Joslin *et al.* (1952) listed a further 20 cases from the New England Deaconess Hospital, and two of these were in children. The first a boy of 12 years, whose resistance lasted for 8–10 days and required a maximum of 210 units daily; the second a girl of 14 years, whose resistance lasted more than one year and whose maximum requirement of insulin was 470 units daily. The boy's resistance was associated with an allergic sensitivity to all insulins except the crystalline variety, and the girl's resistance was associated with abscesses on the thigh.

Although children are commonly classified as insulin-sensitive, it is by no means uncommon for them to require more insulin for stabilization of their blood sugar than would be regarded as their expected pancreatic secretion. Although this insulin resistance is commonly taken to be due to the action of contra-insulin hormones, as in diabetic girls at puberty, there is no objective evidence for this. In fact, the only exact hint regarding the possible mechanisms involved in insulin resistance derives from Bornstein's work (1953). He injected into insulin-resistant patients 300 units of crystalline insulin intravenously, and by his method of insulin assay was unable in one hour to demonstrate any insulin in the plasma.

There is now to be related the unhappy history of a diabetic girl whose insulin resistance was of a degree hitherto unrecorded, and in whom the resistance was phasic. The resistant phases appeared to be premenstrual and the phases of insulin sensitivity appeared to succeed the menstrual flow.

An Extreme Case of Insulin Resistance

A.B., aged 13 years, a grammar-school girl, was admitted to the children's ward of the Derby City Hospital on December 10, 1951, suffering from diabetic ketosis. The symptoms of diabetes had been present for two months. She recovered without the use of intravenous saline and was discharged from hospital on December 23—requiring 24 units of soluble insulin twice daily. Her maternal grandmother was said to suffer from diabetes. Her height at this time was 5 ft. 4¼ in. (164 cm.), which was four inches (10 cm.) above the average height for a girl of her age. The secondary sex characters were just appearing, but menstrual function was not established.

She attended the children's diabetic clinic at the Derbyshire Hospital for Sick Children during the following year and made excellent progress. Her insulin needs were increased to 60 units of soluble insulin daily in two injections. She was readmitted to the Derby City Hospital on January 9, 1952 (thirteen months after her original admission), for restabilization on a mixture of soluble and zinc protamine insulin. Her height had increased in 1952 by ¾ in. (1.9 cm.) to 5 ft. 5½ in. (166 cm.) and her weight was 8 st. 9 lb. (54.9 kg.). The secondary sexual characters were now fully developed, but the menses had not occurred. Early-morning hypoglycaemia developed with a dose of zinc protamine insulin as small as 8 units, so a mixture of globin insulin 24 units and soluble insulin 28 units was used for a time. In six weeks in hospital she had gained 8 lb. (3.6 kg.) in weight, so her daily ration of carbohydrate (which had previously been "free" except for the restriction of jams, sugar, and sweets) was reduced to 250 g.

On February 26, 1953, while still in hospital, persistent hyperglycaemia developed and she was treated by injections of soluble insulin three- to four-hourly. Despite a steady increase of dosage during the next three weeks, to the amount of 12,160 units by March 20, her blood sugar was seldom below 250 mg. per 100 ml. in the daytime, nor did sugar disappear entirely from the urine. There was intermittent

ketosis, but her general condition remained good. During the succeeding few days, because of the difficulty of breaking down this resistance by increased dosage (the injection of 40 ml. daily with an insulin concentration of 320 units per ml. was already creating problems) it was decided to reduce her insulin dosage to 80 units four-hourly. This was continued till March 24, when Professor D. M. Dunlop kindly saw the patient with me and suggested the use of intravenous insulin. For a few hours this procedure was effective and her blood sugar was reduced from 520 mg. at 4 p.m. to 253 mg. per 100 ml. at 10 o'clock the next morning, and a further 80 units of intravenous insulin reduced it to 145 mg. per 100 ml. This success was brief. On March 26 280 units, on the 27th 240 units, on the 29th 420 units, on the 30th 680 units, and on April 1 820 units were given intravenously. On April 2 Dr. Wilfrid Oakley agreed to accept the responsibility for her treatment, and she was admitted under his care at King's College Hospital. She travelled to London by car with her mother and was ill on the journey with some vomiting; on arrival she was acidotic and ketotic but her blood sugar was only 75 mg. per 100 ml. She was treated by intravenous saline, gastric lavage, and small doses of soluble insulin. Insulin sensitivity was restored and she was discharged from King's College Hospital on April 12, having two doses of soluble insulin (28 and 24 units) each day. Insulin sensitivity continued for two weeks, but hyperglycaemia again developed, and it was necessary to readmit her to the Derby City Hospital for treatment of pre-coma on May 16.

On readmission insulin sensitivity was restored by intravenous saline, continued for two days, and a maximum dose of 350 units of insulin in one day. Insulin resistance again developed, and she required intravenous saline on June 2 (two days) and on June 13 (three days). The maximum daily dose of insulin in this month was 800 units on June 8. Hyperglycaemia and ketosis developed again towards the end of the month, and intravenous saline was required from July 3 to 5. On July 6 vaginal haemorrhage occurred for the first time, and from then until July 23 all was quiet and the blood sugar was easily controlled with 100 units daily or less. On July 23 the storm broke without warning; her morning blood sugar was 100 mg. per 100 ml., but by evening she required intravenous saline, which it was necessary to continue for four days. She was very ill and only just survived. There was slight vaginal haemorrhage during the last two days of this ketotic period and menstruation was fully established for two days on recovery.

A quiet month followed, and when the next menstrual period began on August 28 without consequent rise of blood sugar, anxiety was relieved. On the fifth day of the period hyperglycaemia and ketosis developed and intravenous therapy was required for two days. On this occasion insulin sensitivity was not restored, and daily insulin dosage climbed to 9,740 units on September 17, fell, and climbed again to 8,000 units on September 24. This, however, was the first day of a three-day menses, and once again insulin sensitivity was restored.

During the summer both stilboestrol and ethinyl oestradiol were used in treatment, but with no good result that could be seen, and their use was discontinued. As will be readily appreciated, hypoglycaemic reactions gave rise to much therapeutic difficulty when insulin sensitivity was restored with these enormous doses of insulin—and one feature of this hypoglycaemic state which was troublesome was the persistence of "hysterical" hyperventilation long after the acidosis and electrolyte imbalance had been corrected. On another occasion the appearance of meningismus required the performance of a lumbar puncture, as there were cases of lymphocytic meningitis in the ward at the time. The patient was in fact a charming, stable, and intelligent creature, but these violent fluctuations in blood sugar now and again played havoc with her psyche. In July thrombophlebitis and urticaria developed during a ketotic phase, and this trouble, though it recurred later, was never more than might have been expected to result from repeated intravenous therapy and the large doses of insulin employed.

October was an insulin-sensitive month, although her daily needs were between 1 and 200 units. The menses were late, and 13,440 units were required on November 1. Menstruation occurred on the 9th (a six-weeks interval), and on the fifth day of her period she required 7,480 units. On November 27 she required, for the first time in three months, intravenous saline for four days; and on November 30 she had a one-day period. During the month of December her insulin needs increased again to a maximum of 8,640 units daily, but a further complication occurred with the development of abscesses at the sites of insulin injection. These came up slowly, and many of them required incision. Haemolytic streptococci were isolated from the abscesses. Some of the incisions produced only serum and fat globules.

The story of the last two months of her life is told in the Table. Insulin sensitivity was never fully restored in December. Hexamethonium bromide was used in doses of

Analysis of the Last Two Months of Treatment

Date	Urinary Endocrine Assays (24-Hr Periods)				Daily Insulin	Ketosis	Menstruation	Sepsis	I-V. Saline
	Oestrogens	Pregnanediol	17-Ketosteroids	17-Ketogenic Steroids					
		mg.	mg.	mg.	u.				
6/11/53	20 i.u.	0·5	9	18	130	O	9/11/53		
11/11/53			10	16	370	O	↓		
13/11/53			9	20	640	O			
16/11/53	None	0·75			7,480	K	16/11/53		
20/11/53	,,	0·6	9	17	3,840	K			
24/11/53	,,	0·5			19,200	K			27/11/53
27/11/53	50 i.u.	0·7	5	7	11,840	K			↓
30/11/53	40 i.u.	0·9			9,760	K	30/11/53		
5/12/53	Trace		10	23	360	O		5/12/53	30/11/53
6/12/53	,,	0·8	7	3	300	O		↓	
11/12/53					1,680	K		Abscesses	
14/12/53	None				310	O			
16/12/53			4	21	1,800	O			
18/12/53	30 i.u.				280	O	26/12/53	22/12/53	24/12/53
31/12/53			7	4	3,220	O	↓		↓
1/1/54	None				3,840	K			25/12/53
3/1/54	,,				4,800	K	3/1/54		
6/1/54			3	8	510	O			
7/1/54	Trace				960	O			
13/1/54			9	16	1,800	K			

This table relates endocrine output to the menstrual cycle and to the insulin-resistant phases. It will be noted that there is a gap from December 19 to 30, a premenstrual period of progressive ketosis and increasing insulin requirements up to 8,640 units daily, eventually requiring intravenous saline.

25 mg. and 12.5 mg. by injection, with the object of potentiating the effect of insulin, and for a few injections this method appeared to be remarkably effective. It soon failed and was discarded. After the late December period some degree of insulin resistance remained, and, in view of the subcutaneous abscesses at the sites of injection which had already been so troublesome, very large doses of insulin were not used. Ketosis recurred on January 13 and a state of pre-coma required intravenous saline. Insulin was given intravenously, and in one day 18,000 units was administered by this route with proper precautions. The blood sugar fell, but the blood urea mounted and renal failure and anuria supervened. It seems possible that the intravenous administration of insulin accelerated the development of shock nephrosis. Death occurred on January 16. Necropsy showed the characteristic tubular changes in the kidneys, but no structural disease in the endocrine system was discovered.

Discussion

From July 6, 1953, to January 16, 1954, the patient required five periods of administration of intravenous saline. In four instances the intravenous saline immediately preceded menstruation, and on one occasion saline was required on the sixth day of the period. The September and October menses were not preceded by intravenous therapy, but in the nine days preceding the September menstrual period 30,720

units of insulin were given, and in three days (9th–7th days) before the November period 18,200 units were required.

Insulin sensitivity was restored immediately after the July, August, September, late November, and December periods, but after the early November menses, which lasted a week, insulin resistance persisted despite a dose of 19,200 units in one day. With these exceptions it may be concluded that insulin resistance was associated with the pre-menstrual phases and insulin sensitivity with the post-menstrual phases. The pre-menstrual phase of insulin resistance varied from 3 to 18 days and the insulin-sensitive phase from two days (menstrual cycle of 20 days) to five weeks (menstrual cycle 46 days).

There can be little doubt that the insulin resistance was hormonal and related to the pre-menstrual phase of the menstrual cycle. Before menstruation was established in May and June (and in April when she was in King's College Hospital) it appeared that insulin sensitivity was restored by the treatment of ketosis by intravenous saline and by frequent insulin injections. This may well have been an incorrect conclusion, and the restoration of insulin sensitivity may have been dependent on a hormonal change not as yet followed by menstruation. The hormones which might possibly be concerned in such resistance are the growth hormone, the corticosteroids, glucagon, the oestrogens, or progesterone. There is no evidence that the female sex hormones can produce an insulin resistance of this degree. The increased insulin requirements of the diabetic woman in pregnancy are well recognized, but they are not of this grandiose nature despite the much greater formation of sex hormones in pregnancy than occurs in the menstrual cycle. The urinary output of the sex hormones was not increased and there was no correlation between the variations in oestrogen and pregnanediol output and insulin needs (see Table). The considerable fluctuations in the daily urinary output not only of oestrogens but also of 17-ketosteroids and 17-ketogenic steroids perhaps portrays the unstable hormonal state of this pubertal girl which was reflected in the diabetes.

The corticosteroids antagonize indirectly the action of insulin and are gluconeogenetic, but there is now increasing evidence that they are not important in the aetiology of diabetes apart from that occurring in Cushing's syndrome. Cortisone has been frequently used in diabetics with no considerable increase of insulin needs. The 17-ketogenic steroids (Norymberski, 1952) are stated by Norymberski, Stubbs, and West (1953) to represent a little less than half the 17α-hydroxycorticosterone output (hydrocortisone, Kendall's Compound F). There was considerable variation of the corticosteroid output (see Table), and it was sometimes raised above normal levels, but not greatly. Nor was the highest output related to the periods of ketosis, as in the cases reported by Stowers (1951). There is no evidence that the adrenal cortex played an important part in the insulin resistant diabetes of A.B. And the fact, commented on below, that her growth was excessive during the year of insulin resistance speaks strongly against adrenocortical influence.

Glucagon has not established itself as a hormone, nor has its place, if any, in the aetiology of diabetes been determined, so that it may be excluded from consideration. In a series of remarkable researches each new fact sustaining a brilliant generalization, F. G. Young and his colleagues (1951) have proved that the growth hormone is diabetogenic in carnivorous animals. Unfortunately no assay of the growth hormone is available in man, so that clinical evidence in favour of Young's hypothesis is indirect. Priscilla White (1952) was the first to make the observation that the height of diabetic children was greater than average for their age and sex. A.B. was 4 in. (10 cm.) above the average height for her age at the onset of diabetes. In the year of stability, 1952, she grew ¾ in. (1.9 cm.); in the year of increasing insulin resistance, 1953, she grew 2½ in. (6.3 cm.). Nothing is known of the output of the growth hormone in the varying phases of the menstrual cycle; nothing is known of the variations in the internal environment which may affect its output. Nevertheless, there is indirect evidence that the growth hormone was remarkably active in A.B. during 1953.

The development of a local reaction to insulin at the sites of injection, followed by some sepsis, no doubt enhanced the insulin resistance during the last two months of her life. It also had the effect of making me more reluctant to use again the large single subcutaneous doses (10 ml. × 320 units per ml.) which were used in September. The use of intravenous insulin in the final ketotic episode may have hastened the end.

There has been much debate for many years on whether insulin used in excessive doses may itself encourage hyperglycaemia, both in the treatment of diabetic ketosis and in the maintenance therapy of diabetes. The daily injection of insulin in the rat has caused reduction of the growth of the islets of Langerhans (Evans and Haist, 1951), and no one would wish to use more insulin than is necessary to maintain the diabetic's blood sugar near normal limits. There are complicating factors in diabetes—obesity, infection, and electrolyte imbalance—and when these are adequately controlled insulin requirements are reduced. There were, however, other undefined complicating factors as in A.B., and until some other means of opposing them is discovered insulin must be used in dosage which is adequate both to reduce the blood sugar and to prevent ketosis. On many occasions and for long periods frequent small doses of insulin were used in our patient in the hope of not provoking the action of contra-insulin phases. This method was unsuccessful.

Summary

An example of unique insulin resistance in a young diabetic girl is recorded. The maximum daily dose of insulin used was 19,250 units. The resistance was phasic, and when menstruation was established it was seen that the resistant phases were usually premenstrual and the sensitive phases post-menstrual.

A large number of urinary endocrine assays were made, and although these fluctuated considerably they showed no remarkable deviation from average findings.

It is assumed that the growth hormone had a hand in this insulin resistance. The patient was 4 in. (10 cm.) above the average height at the onset of her diabetes, she grew an average amount in a year of stability, but in the year of insulin resistance she grew nearly 2 in. (5 cm.) more than the average for her age—0.7 in. (1.8 cm.).

The correct treatment of insulin resistance is to overcome the resistance by using insulin in adequate dosage.

I am grateful to Dr. W. G. Oakley, who treated the patient in King's College Hospital during one of her ketotic phases; to Professor D. M. Dunlop, who helped me with his experience of insulin resistance; to Dr. C. G. Paine, Mr. F. L. Mitchell, Ph.D., and Mr. M. J. Level, B.Sc., of the Endocrine Laboratory, Jessop Hospital for Women, Sheffield, who performed the urinary endocrine assays; to Dr. Ann Ferguson, paediatric registrar, and my house physicians, Drs. J. Forsyth and M. W. Dickson; and to the sisters and nurses in the children's ward at the City Hospital, Derby, who were unremitting in their care of the patient.

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THE VALUE OF PAPER ELECTROPHORESIS OF SERUM PROTEINS IN DIAGNOSIS OF ASCITES

BY

H. E. M. KAY, M.D., M.R.C.P.

From the Department of Pathology, St. Thomas's Hospital Medical School, London

Changes in the serum electrophoretic patterns, reflecting, as they frequently do, the stage or intensity of a disease rather than indicating its exact cause, are seldom likely to be of great value in a purely diagnostic capacity. Moreover, the absence of literature concerned with clinical application as opposed to method and refinements of electrophoresis is a sign that there is some doubt of its usefulness in this field, and it seems that the wave of initial enthusiasm that greeted the introduction of the paper method is already fast receding. In this context it may be profitable to take a single clinical problem which arises from time to time and which demonstrates the possibilities as well as the limitations of electrophoresis.

One such problem is the patient whose predominant manifestation of disease is ascites. This is most often due to cirrhosis of the liver or peritoneal metastases of carcinoma; less often, a malignant tumour, usually of the liver but without direct peritoneal involvement, is found; while in other cases constrictive pericarditis, cardiac failure, or subacute nephritis may be the primary condition (although in the last-named disorder the diagnosis is seldom in doubt and in cardiac failure ascites is usually an insignificant part of the total syndrome). The distinction between hepatic and malignant disease, however, may be a matter of some difficulty, for, even if other signs and symptoms are present, they are often of a vague nature or are common to both (hepatomegaly, anorexia, haematemesis, etc.).

In these circumstances serum electrophoresis may be a most valuable guide, since the changes in each condition are quite distinct and, as is shown, reasonably constant. Briefly, in chronic liver disease a variable increase of γ-globulin accompanies low or low normal α-globulin levels, while in malignant disease low, normal, or slightly increased γ-globulin levels are overshadowed by a well-marked α-globulinaemia. In constrictive pericarditis and congestive cardiac failure insufficient evidence is available for generalization, but from limited data (Luetscher, 1941, and personal observations), and on theoretical grounds, either a normal pattern or a moderate increase of both α- and γ-globulin might be expected. Intrahepatic secondaries seem, for reasons which will be considered later, to give diverse patterns, while subacute nephritis produces a well-known pattern. In this a prominent band of α-2 lipoprotein is contrasted with a considerable reduction of all other protein fractions. This may resemble the pattern of some forms of malignant disease; the distinction is discussed below.

Methods

Electrophoresis of serum was performed by the method of Flynn and de Mayo (1951)—10 to 20 μl. of serum (20 to 30 μl. of ascitic fluid) being applied to No. 1 Whatman paper. Azocarmine Bx (Turba and Enenkel, 1950) was preferred as a protein stain, since there is less background staining than with naphthalene black, and, unlike bromphenol blue, albumin and globulins take up the stain equally well (that is, in proportion to their nitrogen content). After drying, the paper was cut up into five pieces (corresponding to the protein bands) and the dye was eluted in 5 ml. N/10 NaOH. The optical density of the eluate was determined in a Hilger absorptiometer and the relative concentrations of the protein fractions were determined. Total serum protein was measured by the micro-Kjeldahl method.

Results

Thirty-eight consecutive* cases of ascites have been studied by paper electrophoresis of serum and, in a few cases, of ascitic fluid. In general, serum is preferable, since its higher protein content produces clearer, denser bands and it is usually more easily available. Ascitic fluid, it appears, resembles diluted serum but with relatively more albumin and with globulin concentrations which are less constantly related to the cause of the ascites. The subject has been investigated and discussed by Luetscher (1941). A summary of the serum analyses in the present series is shown in Table I, and from these the most significant results have been plotted in Figs. 1 and 2.

Carcinomatosis Peritonei and Hepatic Cirrhosis

These two major groups of cases are so well defined and divided from each other that comment at this stage is superfluous. However, two cases—one from each group—in which electrophoretic analyses seemed to be partially in conflict with clinical and other laboratory evidence may be worth quoting.

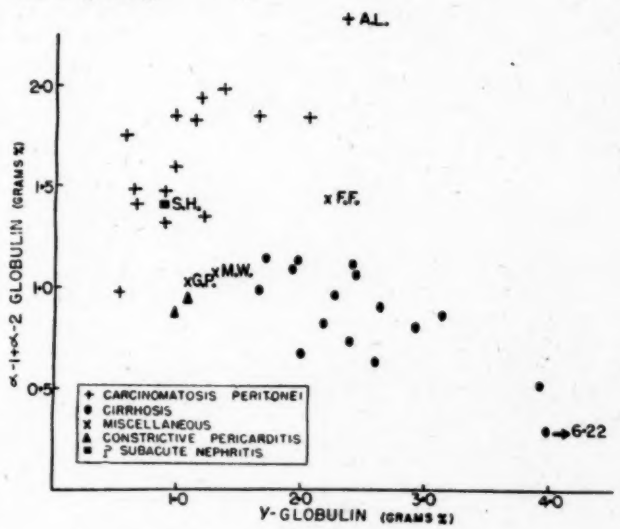

FIG. 1

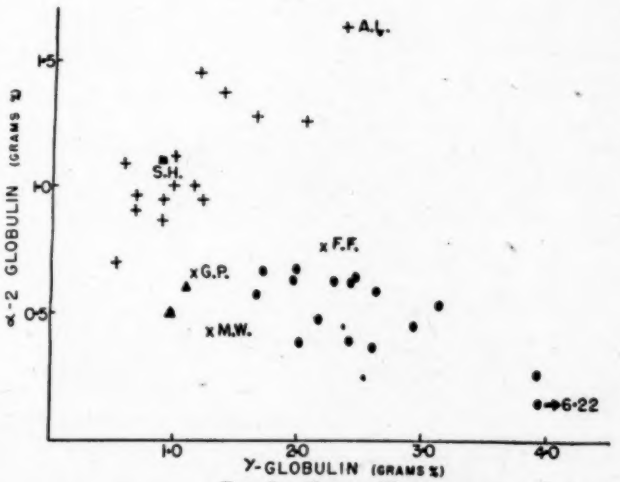

FIG. 2.—Key as Fig. 1.

*Omitting cases of cardiac failure and one case in which the diagnosis is uncertain.

TABLE I.—*Serum Protein Analyses*

Diagnosis	Total	Albumin	Globulin			
			α-1	α-2	β	γ
Carcinomatosis peritonei (15 cases)	6·07±0·79	2·34±0·65	0·56±0·14	**1·10±0·25**	0·93±0·20	**1·14±0·53**
Cirrhosis of liver (16 cases)	6·58±0·72	2·26±0·48	0·36±0·09	**0·50±0·15**	0·81±0·20	**2·65±1·13**
Miscellaneous						
G.P.	5·00	1·70	0·36	0·65	1·20	1·07
M.W.	5·22	1·96	0·65	0·42	0·90	1·29
F.F.	7·60	2·70	0·67	0·76	1·27	2·20
Pericarditis:						
1	6·62	3·94	0·36	0·50	0·87	0·96
2	6·50	3·66	0·34	0·60	0·82	1·08
3	7·20	—	—	—	—	—
? Subacute nephritis S.H.	4·34	1·02	0·29	1·10	1·06	0·87

Serum protein is expressed as g./100 ml. serum with standard deviations of initial groups.

Case 1.—An obese woman of 65 complained of progressive abdominal distension of one month's duration. This was accompanied by a vague feeling of ill-health together with occasional vomiting, and for one week a slight pain in the right side of the abdomen. A mild attack of jaundice at the age of 12 was possibly relevant. Examination revealed a grossly distended abdomen with oedema of the legs and varicose veins. The only other abnormal findings were a blood pressure of 230/120 and doubtful icterus. Laboratory investigations: Hb 79% (Haldane); E.S.R., 35 mm. in one hour (Westergren); blood urea, 23 mg. per 100 ml.; serum protein, 6.2 g.% (albumin 2.1 g., globulin 4.1 g.—sodium sulphate precipitation); alkaline phosphatase, 12 King–Armstrong units; thymol turbidity, 3 units; icteric index, 17 units. Paracentesis produced 14½ pints (8.2 litres) of clear yellow fluid which was thought to contain fragments of a columnar-celled carcinoma. Electrophoresis, however (Fig. 3, A), showed that most of the excess serum globulin was γ-globulin (albumin, 2.21 g.; α-1, 0.35 g.; α-2, 0.62 g.; β, 0.75 g.; γ, 2.27 g.), and at necropsy, several months later, cirrhosis of the liver was found.

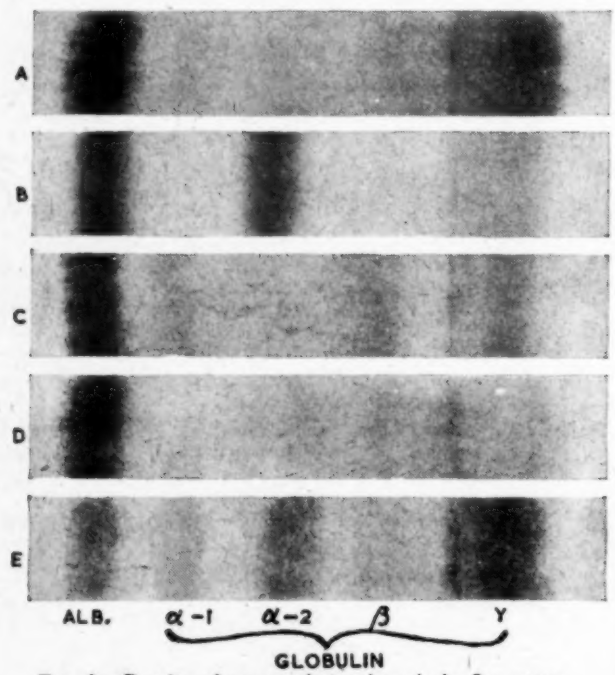

FIG. 3.—Results of serum electrophoresis in five cases.

Case 2.—A woman of 53 complained of intermittent abdominal pain for three days with swelling of the abdomen for two weeks and a cough for one year. An attack of jaundice at the age of 19 had lasted for six weeks. On examination she was pale and possibly slightly icteric, with spider naevi on the face and neck. The only physical signs were distension of the abdomen and shifting dullness. Urine: slight excess of urobilinogen. Blood: Hb, 92% (Haldane); blood urea, 42 mg. per 100 ml.; serum protein, 6.6 g.% (albumin 3.4 g., globulin 3.2 g.—sodium sulphate precipitation); thymol turbidity 2 units; alkaline phosphatase, 13 King–Armstrong units. Faeces showed no occult blood. Paracentesis produced 13½ pints (7.7 litres) of fluid, which contained lymphocytes and endothelial cells only. At this stage a presumptive diagnosis of hepatic fibrosis was made, but electrophoresis (Fig. 3, B) seemed to be against this (albumin, 2.12 g.; α-1, 0.61 g.; α-2, 1.37 g.; β, 1.10 g.; γ, 1.37 g.). Later, after a second paracentesis, a mass was felt in the left iliac fossa, and subsequent laparotomy revealed a carcinoma of the ovary with diffuse peritoneal metastases.

Miscellaneous

In three cases carcinoma of different sites had, without peritoneal metastases, led to the formation of ascites. As their protein analyses differ from both the main groups (see Table I and Figs. 1 and 2) they are worth consideration in some detail.

The first, G.P., with obstructive jaundice of three months' duration prior to the occurrence of ascites, was found at laparotomy to have a carcinoma of the head of the pancreas. It is possible that this caused some degree of portal obstruction; but the patient might also be supposed to have had some degree of biliary cirrhosis and in addition the serum albumin concentration was very low (1.70 g.%). These factors in combination were probably responsible for the ascites.

M.W., with a well-marked α-1 globulinaemia without α-2 globulinaemia, which is most unusual (Fig. 3, C)—died after a short illness marked by fever, jaundice, and hepatomegaly. At necropsy the liver tissue was found to be largely replaced by a mass of growth, judged on histological grounds to have arisen from biliary epithelium. Neither hepatic nor portal veins were thrombosed, so that the same factors were probably operative in producing ascites as in the previous case.

In F.F. a large necrotic carcinoma of the right lower lobe bronchus had infiltrated the right auricle, the diaphragm, and much of the upper part of the liver. Thrombosis of the inferior vena cava had occurred below the level of the renal veins. Microscopy of the liver showed intense centrilobular congestion and necrosis of the adjacent liver cells, but only slight fibrosis. A complicating factor was the presence of rheumatoid arthritis, and with such a combination of conditions almost any sort of protein pattern might be expected. It is perhaps surprising that with so much tissue disorganization and destruction the increase of α-globulin should be so slight. However, if α-globulins do originate in the liver (see below) it is possible that the embarrassment of hepatic function would have inhibited their formation, thus producing a pattern which most closely resembles the group of hepatic fibroses. This last case illustrates clearly the chief limitation of serum electrophoresis—namely, its incapacity in any case of a complicated nature to distinguish the pathological processes that are occurring.

Constrictive Pericarditis

Three patients were found to have constrictive pericarditis, and, whereas two of these had essentially normal protein

patterns, the third serum produced a curious "plateau" pattern from the γ to the α-2 (Fig. 3, D), which completely defies both analysis and explanation.

Subacute Nephritis

Finally, there remains one patient, S.H., in whom the diagnosis is still uncertain; but as the uncertainty may well persist, and as the case raises some points of interest, it seems worthy of quotation.

Case 3.—A woman aged 58 presented with gross oedema of the legs and ascites. Persistent and fairly heavy albuminuria was noted, accompanied by occasional granular and hyaline casts, while the serum contained a reduced protein concentration (4.34 g.%) and raised cholesterol (474–515 mg. per 100 ml.). In addition, however, several tests for occult blood in the stools were strongly positive. Intravenous Congo red was not taken up by the tissues.

The protein strip revealed a pattern that is compatible with either Type II nephritis or malignant disease. Theoretically, these should be distinguishable by determining the nature of the α-2 globulin. In nephritis this is largely lipoprotein; in conditions of tissue destruction (including amyloid disease) it is mainly glycoprotein. On staining with Sudan III and periodic-acid-Schiff the α-2 band turned out to contain polysaccharide rather than fat, which would support a diagnosis of amyloid disease or carcinomatosis. Nevertheless the course of the disease in this patient to date is much more suggestive of nephritis.

Discussion

In considering the results obtained in this investigation three main questions may be posed: How far do they agree with the results of other similar studies?; What are the basic pathological mechanisms underlying the changes described?; and, Are these changes sufficiently constant to be applicable in diagnosis?

The last question may be taken first, and can be answered in the affirmative. Although the number of cases reported is small, they are grouped closely and distinctly enough to include the overwhelming majority of any subsequent cases that might be added to them. Statistical significance is really irrelevant in this situation even though the probability and extent of overlapping in larger series might be estimated. Furthermore, it is suggested that in clinical practice even the analysis of strips is scarcely necessary. For the average case visual judgment will suffice; in the doubtful one, it is unlikely to help. The conclusion that may be drawn is that a clear distinction can be made between ascites due to peritoneal metastases and that due to intrahepatic causes. Furthermore, if taken in conjunction with other tests—especially, for example, the E.S.R. and thymol turbidity—serum electrophoresis will always be found to be of some assistance in the elucidation of peritoneal effusions.

In seeking for corroborative evidence from other sources there is a mass of information to be found on the plasma proteins both in cancer and in liver disease. Winzler (1953), for example, in a review of the former subject, refers to over 300 relevant papers, but of these only one contains comprehensive and detailed observations of electrophoretic analyses. That study (Mider *et al.*, 1950) included 258 patients with uncomplicated cancer which was classified according to the stage of the disease (localized, advanced, and late) and to a certain extent as regards the site (but not the histological type) of the growth. The relevant figures are shown in Table II, and these may be compared with the first part of Table I. Excepting only the γ-globulin levels, there is good agreement, especially with Mider's category of late cancer. The γ-globulin discrepancy may be purely a technical one for which a number of explanations may be offered,* or it may reflect some fundamental aspect of the body's reaction to a particular sort of malignant process. Unusually high globulin levels (probably mainly γ-globulin) have been noted occasionally in malignant disease (Bing, 1940; Snapper, 1943), but, with the exception of myelomatosis, in which the tumour cells undoubtedly produce the abnormal increment, their significance is obscure. The theory of humoral resistance to invasive tumours by means of antibodies is now out of favour, but it is possible that antibody formation may be stimulated by some of the products of tumour breakdown, especially if the peritoneal cavity is acting as a large test-tube in which a variety of cellular disintegrations is occurring.

TABLE II.—*Serum Protein Analyses (From Mider et al., 1950)*

Diagnosis	Total	Albumin	Globulin			
			α-1	α-2	β	γ
Normal	6·52	4·04	0·38	0·66	0·76	0·66
Cancer	6·02	2·94	0·53	0·90	0·89	0·75
Late cancer ..	5·73	2·38	0·65	1·05	0·99	0·82

Of some interest in this connexion was Case A.L., with markedly raised serum γ-globulin (Fig. 3, E). An ovarian carcinoma with widespread peritoneal metastases was demonstrated at laparotomy, but in addition the bone marrow was found to contain some 5% of plasma cells.

Whatever may be the case with γ-globulin, there is little doubt that the presence of a large area of tissue disorganization of destruction is closely bound up with the α-globulinaemia. The association of inflammation and tissue destruction with increase of both α-globulin bands was first noted by Longsworth *et al.* (1939), and many similar observations—for example, of increases of serum protein-bound polysaccharide (most of which occurs in the α-bands)—have since been made. As yet no hypothesis has been advanced to explain the relationship. "The plasma α-globulin levels may reflect the activity of generalized processes such as tissue destruction or replacement" was as far as Winzler could go in 1953.

Synthesis of α-globulins may well occur in the liver. Experimental evidence is scarce and conflicting, but recent isotope studies have clearly demonstrated the hepatic origin of many globulins (Miller *et al.*, 1950). Furthermore, in uncomplicated liver disease in man α-globulins tend to be slightly lower than normal (Martin, 1949), although from the destructive and inflammatory nature of hepatitis one might expect the opposite. The apposite figures in the present series are around "low normal" levels, being of the same order as those of other observers.

The γ-globulin levels, too, are in line with other electrophoretic studies (Gray and Guzman Barron, 1943; Martin, 1949), the variation, with a range of 1.65–6.22 g.%, being characteristically wide. It was noted that some of the lower concentrations, although definitely abnormal, coincided with thymol turbidity readings of 3 or less (that is, within the range of normality). This finding enhances the value of direct γ-globulin estimations, although, as a rule, in chronic liver disease the thymol test is a good guide to the γ-globulin level. What actually determines the level of serum γ-globulin in these cases is still a matter for speculation. Bjørneboe (1950) has suggested antibody formation, and in the case of very high levels—for example, 6–8 g.%—this seems the most probable explanation; moreover, there appears to be some slight correlation between the intensity of the inflammatory reaction as observed at biopsy and the level of γ-globulin. In other cases the failure of the liver to destroy γ-globulin, as suggested by Martin (1949), seems inherently possible, for if, as one might reasonably suppose, there is retardation in the liver of both protein anabolism and catabolism, this would account not only for the low level of albumin and α-globulins which the liver synthesizes but also for the high

*Of all the boundaries of the electrophoretic spectrum, that between the β and γ is notoriously the least well defined. Extrapolation of the ungeometrical curves which form the closely juxtaposed humps in a phoretogram is capable of large inaccuracies, and so is the arbitrary division of the paper strip with scissors. A second possibility is the presence of a small quantity of denatured protein or of protein adsorbed to the filter paper, which, in the method of Flynn and de Mayo, remains in the fast edge of the γ-band.

level of proteins of extrahepatic origin—that is, γ-globulins. Viewed in this light the customary facile explanation of "a compensatory increase" of globulin contains some sense.

Summary

Electrophoresis of serum proteins in 38 cases of ascites revealed distinct and constant patterns in the major groups with hepatic fibrosis or carcinomatosis peritonei. Other conditions, which form a minority of cases, produce less characteristic changes.

The pathological processes underlying these changes are discussed, and the diagnostic value of serum electrophoresis in this context is assessed.

I should like to thank the physicians of St. Thomas's Hospital for permission to investigate patients under their care; more particularly, I am indebted to Dr. J. B. Harman for his assistance, to Professor F. T. G. Prunty for advice, and to Drs. A. Gibson, C. M. Ridley, and J. W. Whittick for supplying sera. My thanks are also due to Dr. A. Paton for his invaluable criticism of the manuscript. The expenses of this investigation were provided partly from the Endowment Fund of St. Thomas's Hospital.

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MULTIPLE VISCERAL LESIONS DUE TO PHENYLBUTAZONE TOXICITY

BY

J. R. NASSIM, B.M., F.R.C.P.
Physician, St. George's and the Royal National Orthopaedic Hospitals, London

AND

THOMAS PILKINGTON, M.D., M.R.C.P.
Medical First Assistant, St. George's Hospital, London

During the past year many reports have appeared stressing the toxic effects of phenylbutazone. Among the most important of these effects have been agranulocytosis, reactivation of peptic ulcer, jaundice, renal lesions, skin rashes, and oedema (Kuzell *et al.*, 1952; Cudkowicz and Jacobs, 1953; Etess and Jacobson, 1953; Stifel and Burnheimer, 1953).

We have recently seen a patient in whom the drug caused multiple visceral lesions and posed problems in differential diagnosis.

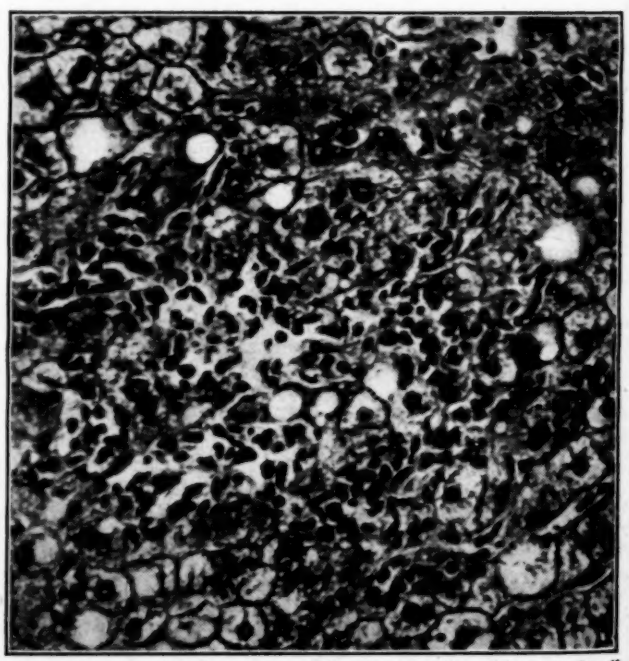
Case Report

A 53-year-old woman attended another hospital in January, 1953, because of severe pain in the right hip due to osteoarthritis. Treatment with analgesics and physiotherapy gave no relief. In April she was admitted to hospital, where she derived some benefit from femoral traction. However, soon after discharge the pain increased and she was given phenylbutazone, 200 mg. thrice daily. A few days later she developed diarrhoea, diagnosed by her own doctor as gastro-enteritis, and treated with kaolin mixture; phenylbutazone was stopped. After the diarrhoea had ceased the patient again took the drug, as it had given her great symptomatic relief. Within a few days she noticed increasing swelling of her feet and legs, and, soon after this, complained of anorexia, headache, pains in the limbs, substernal pain, and fever. Phenylbutazone was again stopped, but her fever and general condition did not improve. On readmission to hospital on June 11, 1953, she was found to be very ill. Her temperature fluctuated between 99 and 101° F. (37.2 and 38.3° C.), the conjunctivae were suffused, a slight erythematous rash was present on forehead and chest, and there was a maculo-papular rash on both shins: the legs were moderately oedematous and the blood pressure was 100/70. There was slight anaemia (Hb 67%) and a sedimentation rate of 65 mm./hr., but the white blood count was repeatedly normal. The urine contained albumin, a trace of bile pigment, a marked excess of urobilinogen, and granular casts. A tentative diagnosis of leptospirosis was made at this stage, but repeated agglutination tests remained negative. On retesting the urine ten days later, it was found to contain large quantities of sugar, and a glucose-tolerance test showed a typical diabetic curve; serum amylase levels were repeatedly normal. She was given 12 units of globin insulin daily until the glycosuria had disappeared 10 days later.

An E.C.G. taken on June 23 because of the chest pain showed: "Sinus rhythm 60/min.; horizontal heart; T waves low in AVL, 1, and inverted in V_{3-6}, consistent with non-specific myocardial changes." Radiographs of the chest remained normal. Repeated liver function tests showed a reversed A/G ratio (3.4 g./4.5 g.), rising thymol turbidity, and positive flocculation reactions.

The diagnosis now seemed to be between viral hepatitis and phenylbutazone poisoning. A liver biopsy (see Fig.) was therefore taken, on which Professor Crawford reported: "Sections show a moderate degree of fat accumulation in the liver cells. Individual cells contain large droplets of fat, and the affected cells are irregularly distributed without any special lobular arrangement. There are numerous foci of focal necrosis into which infiltration with mononuclear cells has occurred, and there is also some accumulation of mononuclear cells in the portal tracts. These appearances suggest toxic damage to the liver, and are consistent with the suggestion that the lesion is due to phenylbutazone." This finding led to the final diagnosis of poisoning with phenylbutazone.

During the second week in hospital the patient's condition improved: the fever subsided and she lost her



Liver biopsy, showing area of focal necrosis with round-cell infiltration. (H. and E. ×200.)

symptoms. At the time of discharge, eight weeks after admission, the glucose-tolerance test was still slightly abnormal and the thymol turbidity appeared to be rising; all other abnormal findings had reverted to normal. Further assessment on September 27 showed her to be in excellent health, but the thymol turbidity had risen further to 7.3 units and her tolerance to glucose was still decreased. In the E.C.G., recovery of the T waves began to take place by July 13, and there was a return to a picture within physiological limits by September 7: "T waves are a little low in $V_{5\text{-}6}$, but within physiological limits."

A follow-up on January 18, 1954, showed normal liver function and glucose-tolerance tests; the urine was clear and the blood pressure was 140/80.

Discussion

The mode of onset of this patient's illness, the findings on liver biopsy, and negative leptospiral agglutination tests seem to permit only a diagnosis of phenylbutazone poisoning, although there were many features which suggested the possibility of leptospirosis or viral hepatitis. Severe toxic reactions due to this drug have been described in about 50% of patients. The involvement of so many different viscera in our patient suggests a hypersensitivity reaction. That such reactions occur in patients receiving phenylbutazone is made extremely probable by the microscopy findings in two fatal cases (Nathan *et al.*, 1953; O'Brien and Storey, 1954). In both patients there were multiple and widespread vascular lesions. There were also granulomatous lesions in many organs, including the pancreas. We know, however, of no other case showing transient hyperglycaemia responding to small doses of insulin.

Reports, so far, have not clarified the nature of the jaundice sometimes observed. Bourne (1953) reported three patients in whom the lesion appeared obstructive, and in another—not clinically jaundiced—granulomatous lesions were found in the portal tracts (O'Brien and Storey, 1954). In our patient the hepatitis appears to have been definitely toxic in nature.

The danger of continuing phenylbutazone after the occurrence of slight symptoms—in this case diarrhoea—must once again be emphasized.

Summary

A case of severe phenylbutazone toxicity is described. The manifestations were toxic hepatitis, myocarditis, renal lesion, glycosuria, in addition to gastro-intestinal upsets, oedema, and skin rash.

There has been complete recovery.

We are very grateful to Professor Crawford for the photomicrograph of the liver biopsy and to Dr. A. W. W. B. Woods for the electrocardiographic reports.

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Liverpool health visitors, according to the recently published report of the principal school medical officer, are unanimously of the opinion that television is playing a large part in cases where children do not receive sufficient sleep. As Professor Semple points out in his report, children who formerly were out in the streets until a late hour now have the alternative attraction of staying up late to watch television. One health visitor has found that when she advises parents to send their children earlier to bed she is frequently met with the mother's frank admission that the children are beyond her control.

FOETAL DEFECTS FOLLOWING INSULIN COMA THERAPY IN EARLY PREGNANCY

BY

IAN G. WICKES, M.D., M.R.C.P., D.C.H.

Paediatrician, North Middlesex Hospital and South-east Essex Group

When Duraiswami (1950, 1952) described his experiments on developing chick embryos in which he produced skeletal and ocular defects by the timed injection of insulin, he added yet another possible aetiological agent in the genesis of congenital deformities to the long list which had already been compiled by Warkany (1947). He showed that a single injection within the first 48 hours after the start of incubation was likely to produce a defect in the vertebral column, whereas on the third day only the claws were liable to be affected. Furthermore, some of these induced defects were subsequently passed on to the next generation. The importance of the timing of these injections corresponds with the known fact that rubella is likely to harm the foetus only if it occurs within the first three months of pregnancy (Gregg, 1941; Swan, 1949).

In man the opportunities for similar experiments do not arise, but the widespread use of insulin as a therapeutic agent might be expected to cause similar complications. The incidence of congenital deformities in the babies born to diabetic mothers is high, but Oakley (1953), who found them in 8.6% of his series, commented that there was no evidence that hypoglycaemia was more frequent or more severe than in those pregnancies that resulted in normal infants. That insulin can hardly be incriminated here is also demonstrated by the physical anomalies and excessive foetal loss rate found in a high proportion of the pregnancies of prediabetic mothers (Gilbert and Dunlop, 1949).

There is one set of circumstances, however, in which excessive doses of insulin may be given for a prolonged period—namely, in the treatment of schizophrenia—and this therapy may occasionally coincide with early pregnancy, as in the following case.

Case 1

A woman suffering from schizophrenia was admitted to a mental hospital on September 28, 1949. She was given a course of deep insulin from October 12 to December 3 with 35 comas and one general convulsion, followed one month later by two E.C.T.s. Pregnancy was not diagnosed until February 3, 1950.

A child was born on April 27, weighing 6 lb. 4 oz. (2.8 kg.), four weeks before the date estimated by the consultant obstetrician. The delivery was normal, but an abnormality of the eyes was soon noticed, and tentative arrangements were made for the baby to attend an ophthalmic clinic. The grandmother cared for the baby and evidently did not seek further advice until she saw the family doctor, who referred the child, aged 3 years, to my clinic. He was blind in the left eye, had some vision in the right, was unable to feed himself, talk, or stand, and was doubly incontinent. The mother had seven normal siblings, and all four children born to them were normal, but nothing is known of the father.

On examination the child presented a picture of severe mental deficiency with wide separation of the orbits and asymmetrical development of the skull, the overall circumference of which was 20½ in. (52 cm.). There was a divergent squint with bilateral optic atrophy, but some apprecia-

tion of light in the right eye. There were no signs of deformities elsewhere, and a complete radiological examination of the whole skeleton revealed abnormalities only in the skull. Dr. Kemp Harper kindly examined the films, and reported as follows: "The films show a deformed skull resulting from premature closure of the metopic part of the sagittal suture with resulting overgrowth of the parietal and occipital regions. The temporal fossae also bulge anteriorly and laterally, and there is an increase in the space between the orbits, probably resulting from overgrowth of the lesser wings of the sphenoids, and with this, or as a result of it, overgrowth of the ethmoids."

Other Case Reports

A number of mental hospitals and psychiatrists with extensive experience in this field have been asked for details of similar cases, but only two have been forthcoming in which pregnancy and insulin coma therapy were known to coincide. Dr. G. S. Nightingale supplied the following case histories.

Case 2.—This patient received insulin coma therapy and E.C.T., which apparently resulted in spontaneous miscarriage before coma level had been reached. She was probably about six weeks pregnant at the time.

Case 3.—This patient had 27 insulin comas before pregnancy was diagnosed. Therapeutic termination was carried out, a normal foetus of about 26 weeks' gestation being removed. Therapy was applied between the seventeenth and twenty-fourth weeks.

The literature has been searched, and the accompanying Table has been compiled showing the available data concerning the previously reported cases and including the three reported above.

Reported Cases of Insulin Coma in Pregnancy

Author	Treatment			Result
	Stage of Pregnancy when Started	Details	Duration	
Gralnick (1946)..	4–8 weeks	Insulin × 25 (14 comas)	6 weeks	Full-term macerated foetus
Nightingale (1953)	<8 „	Insulin × 1	5 days	Spontaneous abortion
Wickes (1954) ..	8 „	„ × 35	7 weeks	Mental defect; skull deformities
Gralnick (1946)..	10 „	„ × 18 (8 comas)	4 „	Full-term macerated foetus
McConnell (1945)	10 „	Insulin	—	Normal baby
„ „	14 „	„	—	„ „
Nightingale (1953)	17 „	„ × 27	7 weeks	Therapeutic abortion; normal foetus
Goldstein *et al.* (1941)	>14 „	"Metrazol." Insulin	2 „	Normal baby

Examination of the data so far accumulated suggests that the tenth week of pregnancy is the critical stage; if treatment is given before that time foetal abnormalities are to be expected, whereas after that week the foetus appears to be no longer vulnerable.

Discussion

That insulin was responsible for the defects described in Case 1 can only be surmised. It is possible that defective germ plasm was present from the start. However, schizophrenic women do not appear to be particularly prone to produce abnormal offspring (Canavan and Clark, 1936). Hyperteleorism may be a familial disorder, but there is no evidence of genetic influence in about 60% of the cases (Brown and Kemp Harper, 1946). It is due to a defect of the sphenoid bone (Greig, 1924) occurring before ossification begins in the ninth week. In Case 1 insulin was given in the eighth week, at a time when the chondrocranium is in a vulnerable state.

Other forms of shock therapy are said not to harm the developing foetus, but there seems to be no record of E.C.T. having been given before the tenth week (Boyd and Brown, 1948). Epilepsy is also thought to be harmless in pregnancy. The above episodes are more short-lived than insulin coma therapy, and it is possible that the harmful effects of the latter are due to anoxia rather than to a specific interference with foetal tissue carbohydrate metabolism, which is the presumed mode of action in the experimental work.

Since insulin coma therapy is very rarely given in early pregnancy it is hoped that in the future the effect on the foetus will be reported in every case, so that the likelihood of the findings here reported being due merely to coincidence may be more accurately assessed.

Summary

The case is described of a mentally defective child with hyperteleorism and optic atrophy who was born to a schizophrenic woman who had received insulin coma therapy from the second month of pregnancy.

Reasons have been given for believing that insulin (or possibly the anoxia induced by it) was responsible for the foetal defects.

A study of the small number of previously reported cases suggests that insulin may be injurious only when given before the tenth week.

I am most grateful to Dr. J. S. Harris for providing me with details of the treatment of the mother in Case 1, to Dr. G. S. Nightingale for searching the files and allowing me to include Cases 2 and 3, and to a number of mental hospital superintendents and psychiatrists who have kindly searched in vain at my request for similar cases. I would also like to thank Dr. R. A. Kemp Harper for his *x*-ray report.

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THE LIVER IN ULCERATIVE COLITIS

BY

R. G. F. PARKER, M.B., B.Chir.

AND

E. J. C. KENDALL, M.B., M.R.C.P.

(From the Bernhard Baron Institute of Pathology, the London Hospital)

There have been many reports in recent years of liver damage as a complication of ulcerative colitis, and occasional references may be found in the earlier literature. The three hepatic lesions most often described are fatty change, severe inflammation in and around the portal tracts, and cirrhosis. Opinions on the frequency and significance of these changes have varied, however, and in particular the occurrence of cirrhosis has been questioned (*British Medical Journal*, 1949). We therefore decided to review all cases of ulcerative colitis which had come to necropsy in the Bernhard Baron Institute of the London Hospital from 1914 to 1953 inclusive, with especial reference to the incidence of liver lesions and the correlation of such lesions with the available clinical data.

There were 73 cases of ulcerative colitis in the years under review. Macroscopic descriptions of the liver

were available in all, but histological preparations were made in 39 cases only. Unless otherwise stated, therefore, the observations which follow are confined to this latter group of cases.

Pathological Findings

The incidence of the three lesions most commonly described in the literature is considered first.

Fatty Change.—The fatty livers encountered have been graded arbitrarily into mild, moderate, and severe cases. In mild lesions the fat was usually present in small foci in occasional lobules only; sometimes, however, it was more evenly distributed. In moderate cases the change was more severe and more diffuse, but less than half the parenchymal cells were affected. In severe cases at least half, usually three-quarters or more, of the liver cells were distended with large fat globules. Where a zonal distribution could be made out, the central zone was usually spared. This was not invariable, however, for in one severely affected liver the midzone was least involved, and in some mild cases the fat was confined to the central zones.

Using the above criteria, there were 25 cases in which fatty change was either absent (8) or of mild degree (17), 5 cases in which it was of moderate degree, and 9 cases in which it was severe. In one severe case, however, the patient had committed suicide by swallowing ammonia when the colonic lesion was in a healing phase, and the fatty liver was probably due to this poison.

Inflammation.—Severe diffuse inflammatory cell infiltration of the portal and periportal tissues was not present in our material. In only six cases was there a degree of cellular infiltration in excess of that so commonly seen at necropsy, and in these only a minority of portal tracts were affected—sometimes only one or two in an entire section.

Cirrhosis.—In only one of the 39 cases was a significant degree of fibrosis present. In this patient there was a carcinoma of the extrahepatic bile ducts which had caused obstructive jaundice and a suppurative cholangitis. The cirrhosis here was almost certainly of biliary type. Of the remaining 38 cases there was a slight fibrous thickening of occasional portal tracts in 4, but in none was there linking up of adjacent tracts or disruption of the lobular pattern of the liver. Cirrhosis was not found macroscopically in any of the 73 patients.

Other Lesions.—In 5 cases there were focal necroses or irregularly distributed centrilobular necroses; in one there was severe amyloidosis; in 2 there were partly organized thrombi in the left hepatic vein; and in 2 there were thrombi in branches of the portal vein. In 2 of the 73 cases examined macroscopically there was a carcinoma of the colon. Neither had hepatic secondaries.

Clinical Correlation

There were no detailed studies of liver function in the series, and clinical evidence of hepatic involvement was scanty. Moderate enlargement of the liver was recorded in four cases, in one of which there was severe fatty change at necropsy. In no case was there jaundice or splenomegaly. Of the seven cases with oedema only two had fatty livers; one of these two had a total serum protein of 3.5 g.%. In another case with oedema but without a fatty liver the serum protein was 5.9 g.%.

Since the hepatic lesion most often found at necropsy was fatty change, the clinical records were examined for factors which might cause this lesion in severe degree. After eliminating cases with coincident disease which might have damaged the liver, there remained for comparison 8 cases with severe fatty livers and 27 with moderate or minimal fatty change. Of these 35 cases 28 were in females and 7 in males, all the severely fatty livers being found in females. This difference in sex incidence is not, however, statistically significant. The onset of the disease was related to childbirth in three of the severely fatty group, diarrhoea being first noted during pregnancy in two cases and in the puerperium in one. All these three cases ran a rapidly progressive course, death occurring in from three to nine weeks after delivery.

The total duration of the disease was very variable and there were frequent long remissions. Of the six cases of longest duration (2 to 4½ years) only two had severely fatty livers. The terminal attack lasted from 5 to 84 weeks and there was no correlation between the length of this final episode and the degree of liver damage. It may be noted here that in six other cases in the series, excluded from this comparison because of coincident disease (2) or lack of histological preparations (4), the duration of the disease was from 7 to 29 years.

Other factors for which no significant differences could be detected between the two groups were severity of diarrhoea, loss of weight (estimated as a percentage of the standard weight for the height and age), and degree of anaemia. Anorexia was more frequently noted in the severely fatty group, as was vomiting, especially towards the termination of the illness. In no patient on whom laparotomy was performed shortly before death was there a severely fatty liver.

Discussion

Fatty change, the most common hepatic lesion found by us, was present in severe degree in 24% of the cases examined microscopically. But since it was not noted macroscopically in the remaining 34 cases, its true incidence was probably no greater than the 15% reported by Kimmelstiel *et al.* (1952) and certainly less than the 55% of Warren and Sommers (1949). Analysis of the clinical records threw little light on the pathogenesis of the lesion except that recent pregnancy was probably a contributory factor in three cases and that anorexia and vomiting may have played a part. There was no correlation between the degree of fatty change and the severity of the intestinal lesions as estimated clinically or at necropsy. It is possible that more detailed knowledge of the patients' diet would have proved fruitful.

We found no evidence to support the view of Cain and Cattan (1937) that liver failure was the main cause of death in ulcerative colitis. But while we would agree with Hardy and Brooke (1952) that the fatty livers usually produce no clinical symptoms, we regard it as probable that liver function tests would have revealed some abnormality in the more severely affected cases.

The incidence of inflammatory cell infiltration was less than we expected; for severe inflammation of the portal tracts and surrounding parenchyma has been described by several investigators, who have called it acute interstitial hepatitis (Lister, 1899), toxic hepatitis (Ross and Swarts, 1948), pericholangitis (Jones *et al.*, 1951), or interlobular hepatitis (Kimmelstiel *et al.*, 1952). In the degree found by us it would seem highly unlikely that it could interfere materially with liver function or, as has been suggested by Kimmelstiel and his colleagues, that it could eventually lead to cirrhosis. In none of our cases was there a frank portal pyaemia, a condition which has occasionally been reported as complicating ulcerative colitis (Felsen and Wolarsky, 1950; Jones *et al.*, 1951), but which is generally acknowledged to do so only rarely.

The absence of cirrhosis in our series is of interest in view of the conflicting opinions on the significance of this lesion as a complication of ulcerative colitis. A number of individual case reports have given rise to the impression that patients with ulcerative colitis are especially liable to develop cirrhosis; but in the majority of reported series (Tumen, *et al.*, 1947; Pollard and Block, 1948; Warren and Sommers, 1949; Jones *et al.*, 1951; Hoffbauer *et al.*, 1953) the incidence is only between 3.3 and 5.7%. Kimmelstiel *et al.* (1952) give a lower incidence still—namely, 1.1%. The interpretation of these figures is difficult. Tumen and his colleagues, for instance, stated that cirrhosis was present in from 1 to 6% of their routine necropsies, and yet they considered their incidence of 3.3% to be significant. Jones *et al.*, on the other hand, maintained that their figure, also 3.3%, was not in excess of that found in routine necropsies

at the Mayo Clinic. Yet Kleckner *et al.* (1952) subsequently reported cirrhosis in 18.7% of biopsy material from this same clinic.

Our series is comparable in size to those previously reported, the largest of which is composed of 93 cases. The average duration of symptoms, too, was not significantly shorter in our patients. We consider, therefore, that our figures lend strong support to the view that the incidence of cirrhosis in ulcerative colitis is not materially greater than its incidence in the population as a whole. Many of the reported cases are probably examples of post-hepatitic cirrhosis, as the clinical histories and necropsy findings not infrequently suggest.

Summary

The liver lesions in 73 cases of ulcerative colitis coming to necropsy in the Bernhard Baron Institute of the London Hospital in the years 1914 to 1953 have been studied.

Severe fatty change was present in 9 of the 39 cases examined microscopically; in one of these, however, it was attributable to exogenous poisoning. Apart from recent pregnancy in three cases, and possibly anorexia and excessive vomiting in others, no clinical factors predisposing to the lesion were found.

Inflammatory cell infiltration was minimal, and, except in one case with biliary obstruction, cirrhosis was not present. It is concluded that there is little if any increased liability to the development of cirrhosis in patients with ulcerative colitis as compared with the population as a whole.

We wish to thank Professor Dorothy S. Russell and Dr. W. W. Brigden for their helpful criticism.

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Medical Memoranda

Sensitivity to Penicillin Causing an Acute Abdominal Emergency

Reactions to penicillin occur in 1.5 to 5% of cases (Keefer and Anderson, 1950). Many are trivial, the most frequent being an urticarial rash. Other reactions described include arthralgia, lymphadenopathy, fever, and oedema (Humphreys, 1951; Wilkes, 1951). More recently fatal anaphylactoid reactions have been reported (*British Medical Journal*, 1951; Thompson, 1952; Pick and Patterson, 1953; and Mayer, 1953), and there has been an increasing correspondence about near-fatal anaphylactoid reactions.

The following case is reported, in which, after an injection of crystalline penicillin, a young woman developed severe abdominal pain and, later, urticaria, oedema, arthralgia, and lymphadenopathy.

Case Report

A married woman aged 28, in the second day of the puerperium after a normal delivery, developed a small whitlow. She was given a parenteral injection of 300,000 units of crystalline penicillin. There was no immediate reaction, but the next morning she complained of severe pain at the site of injection; the area was found to be red and swollen. It was then discovered that when she had received penicillin in 1948 her eyes and tongue had become swollen and large weals had arisen on her arms and legs.

Four hours later, 24 hours after the penicillin injection, she developed severe generalized abdominal pain, and her temperature rose to 100° F. (37.8° C.). Shortly afterwards intractable vomiting started. Tenderness and rigidity were generalized, but apparently were more marked in the right iliac fossa. A tentative diagnosis of acute appendicitis was made.

At laparotomy a normal appendix was found, but some 6 in. (15 cm.) of small bowel presented which was dark purple in colour, fading into normal-looking bowel at either side. The related omentum was swollen and haemorrhagic, and some turbid fluid was present in the peritoneal cavity. As the affected bowel appeared to be rapidly becoming necrotic, and the process seemed to be extending alarmingly, a resection was performed, including several inches of normal bowel at each side. An end-to-end anastomosis was made.

The post-operative period was stormy. Gross oedema of the periorbital tissues, face, hands, and feet developed almost immediately. Elbow, knee, wrist, and ankle joints became swollen and acutely painful. The tongue became swollen, and a generalized urticaria appeared; cervical and axillary lymph nodes became palpable, also the lymph nodes draining the site of the original penicillin injection. Under treatment with antihistamine drugs, adrenaline, and intravenous glucose-saline, the oedema slowly subsided. Four days later the joints became painless, and from that time she made a rapid recovery.

Approximately 19 cm. of small bowel, with frank purpuric haemorrhage into the mesentery and local subserous spread over the bowel, was removed. The muscularis and mucosa appeared normal. Histological examination confirmed the capillary haemorrhage into the mesentery and subserous layer of the bowel. In addition, there was acute congestion of the submucus layer, with oedema of all layers, including the muscle.

Comment

Both the naked-eye and microscopical appearances of the resected portion of the bowel were those of extensive capillary haemorrhage into the mesentery and subserosa. These findings are similar to those seen in Henoch–Schönlein purpura—one of the anaphylactoid purpuras. These appearances, combined with oedema, arthralgia, and urticaria, make it certain that the purpura in this case was due to penicillin sensitivity.

Anaphylactoid purpura has already been reported in a patient receiving penicillin (Anderson, 1947). In the present case no skin purpura was seen before or after the acute abdominal episode, the reaction being confined to a small area of intestine.

In retrospect, resection would seem to have been the correct treatment in this case, despite the normal appearance of the mucosa. As in other intestinal purpuras, necrosis may well have occurred, and it appeared imminent at laparotomy.

I am grateful to Mr. L. A. Cruttenden for permission to publish this case, and to Dr. R. T. Cooke for providing an opportunity of studying the specimen of bowel.

W. J. S. Still, M.B., Ch.B.,
Registrar, Department of Pathology,
Dryburn Hospital, Durham.

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A Fatal Attack of Cyclic Vomiting

A fatal outcome in cyclic vomiting is so unusual that the following case is worth recording.

Case Report.

A 4½-year-old girl was admitted to hospital in coma on March 21, 1954. Since the age of 2½ years she had suffered from periodic attacks of vomiting, having about five attacks each year. Most of them were preceded by a throat infection with fever at the onset. She was admitted for barium *x*-ray studies in May, 1953, and any possibility of malrotation of the intestines was excluded. This investigation provoked a sharp attack of vomiting with ketosis, possibly a combined result of preliminary starvation and of apprehension, and on this occasion there was no fever. Her parents were advised how to minimize the attacks by limiting the fat intake and were told to give liberal quantities of glucose if one seemed imminent. Her doctor was advised to prescribe phenobarbitone when necessary. These measures had led to a lessening of the frequency and severity of the attacks; but on March 20, a few days after developing a cold, she suddenly became irritable and lethargic and refused to eat. By 4 p.m. she had begun to vomit. Her mother encouraged her to have frequent glucose drinks, but she vomited repeatedly through the night, and by next morning had become drowsy. With continued vomiting her drowsiness increased until by 4 p.m. on March 21 she was drifting into coma with rapid, deep, and noisy breathing. At 7 p.m. there were twitching movements of the left side of her face and the left arm and leg. Her doctor administered phenobarbitone, ½ gr. (32 mg.), and sent her to hospital, where she was admitted at 10.20 p.m.

Diabetic coma was suggested by characteristic Kussmaul air-hunger respirations, a strong smell of acetone in the breath, sunken eyes, and dehydration; but her pulse was full and of normal tension, and though her urine was loaded with ketone bodies there was no trace of sugar. Her temperature was 104° F. (40° C.), her throat was injected, and there were a few enlarged cervical lymph nodes. Both eardrums were inflamed. In the chest there was diminished movement on the right but no detectable difference in the percussion note. Breath sounds were diminished over the right upper zone in front and there were coarse crepitations in this area. The abdomen was retracted and soft, and contained no palpable mass. The liver edge was just palpable below the costal margin. There were no convulsive movements, but the eyes were deviated to the right and the left arm and leg were rigid. Plantar responses were both "extensor." The cough reflex was still present.

It was assumed that an acute respiratory infection had induced a severe attack of cyclic vomiting and with the excessive ketosis she had become comatose. Signs in the chest indicated a right upper lobe pneumonia, afterwards confirmed by *x*-ray examination. Immediately after admission intravenous fluids were given and intramuscular penicillin therapy was begun (250,000 units six-hourly). The air passages were sucked out frequently. With the drip running at 150 ml. an hour, she first received 300 ml. of ¼ N saline with 5% glucose, and afterwards 500 ml. of a solution containing sodium lactate (1.68 g.) and sodium chloride (2.93 g.) to which ampoules of glucose were added up to 7.5%. Shortly after admission she vomited a small quantity of bile-stained fluid, and then slight convulsive movements of the left face, arm, and leg began. These recurred frequently during the night and were controlled to some extent by intramuscular paraldehyde or sodium amylobarbitone.

The blood chemistry at 9.15 a.m. on March 22 was: plasma potassium, 14.9 mg. per 100 ml. (3.8 mEq per litre); sodium, 316 mg. per 100 ml. (137 mEq per litre); chloride, 389 mg. per 100 ml. (109 mEq per litre); blood urea, 49 mg. per 100 ml.; blood sugar, 115 mg. per 100 ml.; alkali reserve, 31 vols. CO_2%. (When these estimations were made the child had already had 10 hours' intravenous therapy.) A lumbar puncture at 10 a.m. showed: pressure, 240 mm. water; clear fluid; cells, 5 per c.mm.; protein, 20 mg. per 100 ml.; sugar, 116 mg. per 100 ml.; chlorides, 720 mg. per 100 ml. A nasopharyngeal swab grew *H. influenzae* on culture. The urine was very scanty; a catheter specimen obtained at 12 noon was acid, and contained abundant ketone bodies, chlorides, no sugar.

At 12.30 p.m. she began to receive 200 ml. of 3% sodium bicarbonate, the calculated amount required to restore the alkali reserve to normal. But though a figure of 53 vols. CO_2% was attained, there was no change in her clinical state except that the twitching movements ceased temporarily. This was again noticed when a further 200 ml. of sodium bicarbonate was given later in the afternoon. Air-hunger persisted unaltered until 9 p.m., when the respirations suddenly slowed and then ceased altogether.

At necropsy no abnormalities of significance were found, apart from a slightly enlarged fatty liver and obvious bronchopneumonia mainly involving the right upper lobe. Histology of the liver showed cloudy swelling and fatty change. Cultures from various organs, including the lung, were all sterile.

Comment

Periodic, recurrent, or cyclic vomiting is the description given to periodic attacks of vomiting associated with large amounts of ketone bodies in the blood and urine which occur in certain children, usually between the ages of 2 and 10 years. First described in 1861, and redescribed by Gee (1882) under the heading "Fitful and Recurrent Vomiting," the condition received wider recognition in this country following the writings of Langmead. The early descriptions have really never been bettered, but now the attention is focused less on the fats and more on a probable fault in the carbohydrate metabolism. Attacks are usually benign, with spontaneous recovery in three or four days, but a fatal outcome is possible, and has been recorded in about 20 instances.

Graham (1951) could find no record of a death from this cause at the Royal Hospital, Glasgow, up to 1951, but Still (1924) had observed three fatal cases; and other fatalities have been described in this country by Langmead (1905, 1907, 1912), Parsons (1911), and Hodges (1932). In all these cases the clinical picture was much the same as in the present one, necropsy revealing only fatty change in the liver as the constant finding. Edsall (1903) first drew attention to the close similarity between the state of severe cases and diabetic coma: respiratory difficulty of the air-hunger type occurs, drowsiness deepens into coma, there is much dryness and thirst, the breath reeks of acetone, and the urine differs only in the absence of sugar.

This case reveals the extreme sensitivity of these patients to infection and the rapidity with which seemingly irreversible biochemical changes may result, so that even with intravenous therapy and antibiotics death may still occur. It is likely that, as van Creveld (1952) suggests, cyclic vomiting is a syndrome depending on constitutional and exogenous factors. To the latter belong acute or chronic infections, exertion, excitement, a faulty diet, food allergy, and anaesthetics, any one of which might release an attack. The constitutional weakness seems to be an oversensitiveness to a temporary lack of carbohydrates. Van Creveld also points out that glucose given late in the condition is of little benefit in relieving the ketosis.

I am indebted to Dr. Wilfrid Sheldon for permission to publish this case and for his helpful advice.

R. J. K. Brown, M.B., M.R.C.P., D.C.H.,
Senior Registrar, Children's Department,
King's College Hospital.

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Reviews

BLOOD GROUPS IN ANTHROPOLOGY

The Distribution of the Human Blood Groups. By A. E. Mourant, M.A., D.Phil., D.M.(Oxon). Foreword by Professor H. J. Fleure, F.R.S. (Pp. 438+xxi. 42s.) Oxford: Blackwell Scientific Publications. 1954.

This work on the geographical and anthropological aspects of recent work on the human blood groups supplies an admirable complement to the authoritative work of Race and Sanger on the genetical and serological aspects. The fact that its appearance follows shortly on that of the *second* edition of the latter is a measure of the magnitude of the task which Dr. Mourant has undertaken and so splendidly accomplished.

The structure of the book must have required careful thought. Chapters II to VII review the blood-group systems now known, mostly discovered in the last ten years, and a few auxiliary genetic factors giving simple Mendelian ratios. The next seven chapters constitute a survey by areas of the human populations of different parts of the world. The five chapters that follow give technical information on special problems, thus: Chapter XV, the blood grouping of bone and tissue specimens; XVI, the blood groups of animals and their relation to those of man; XVIII, the collection, preservation, and transport of samples for blood grouping; and XIX, gene-frequency calculations. These all contain information essential to the business of future fact-finding and are not at all easy to fit into a connected treatise. The effect of discontinuity is enhanced by Chapter XVII ("An Attempt at a Synthesis") finding itself in the midst of such miscellaneous material. This chapter is really a discussion of some points in the population genetics of Man, a subject to which blood-group anthropology is bound to make a most fundamental contribution, and would indeed already bear a more extended treatment. Perhaps the author's general findings and principles of interpretation could be expanded to two or more chapters. The other four chapters of this part of the book could well be made accessible as appendices.

The second half of the book starts with a magnificent bibliography, which must have been awaited as impatiently as any part of the book. It runs to nearly 100 pages and contains 1,716 references. The bulk of it is in alphabetical order by authors, but two supplements have been added with about 235 titles, which have to be consulted separately. Then follow nine folding maps and 84 pages of frequency tables reduced from the whole corpus of existing published frequencies. There are two indexes to the bibliography, topographical and zoological, and one general index to the text.

The really immense wealth of tabular material provided has confronted the author with a most difficult problem. The form adopted has been to present percentages even for the observed phenotypes. The reviewer rather regrets that the numbers actually observed in each class have thus disappeared, though since two decimal places have been given they can be reconstructed. For example, Kirkpatrick's new data for Northern Scotland appear with but slight modification as:

Population	Number Tested		O	A	B	AB
Stornoway ..	200	Obs.	50·00	32·00	14·50	3·50
		Exp.	50·19	31·80	14·29	3·73
Sutherland and Caithness	153	Obs.	50·98	32·03	13·73	3·27
		Exp.	51·16	31·83	13·52	3·48
Eastern Ross ..	645	Obs.	58·76	28·06	10·70	2·48
		Exp.	58·58	28·25	10·90	2·27
Inverness West	440	Obs.	59·32	30·68	7·95	2·05
		Exp.	59·14	30·87	8·15	1·84
Inverness East	2,610	Obs.	51·23	34·25	11·84	2·68
		Exp.	51·59	33·87	11·43	3·12

whereas they could equally have been shown as:

Population	Number Tested	O	A	B	AB
Stornoway ..	200	100	64	29	7
Sutherland and Caithness ..	153	78	49	21	5
Eastern Ross ..	645	379	181	69	16
Inverness West	440	261	135	35	9
Inverness East	2,610	1,337	894	309	70

with, what I have omitted on the right, calculated gene frequencies as percentages, and with some indication that each series agrees well with Mendelian expectations, that the five series are not homogeneous, and that the aggregate has the not unusual feature of a sub-significant deficiency of Group AB.

I believe statisticians in general would have welcomed the retention of the raw counts. It is, however, obvious that the author has given all possibilities the most careful consideration, and it would be entirely ungracious not to recognize the indefatigable labour that has been expended in the calculations associated with each body of data.

The maps are most impressive of the extent of the material they embody. They do not, however, open out so as to be visible when the text is being read. The reviewer's reaction was to cut them out, photograph them for lantern slides, and reattach them with an extra fold of plain paper.

Extreme care has been given to accuracy and clarity of exposition, and, indeed, in a book which for its world coverage will certainly be needed and used in remote parts such care is exceptionally necessary. The reviewer has noted one preposterously irritating slip, where on page 4 there is an allusion to "the ability to smell phenylthiocarbamide." Though this is in the introduction, it should scarcely mislead, as the tasting of phenylthiocarbamide and the smelling of hydrocyanic acid are treated, of course correctly, in their own sections.

The chapter on gene-frequency calculations presents simple and useful methods, but is marred, to the reviewer's mind, by an excessive touchiness in regard to the fact that with more computational labour more accurate results could certainly be obtained than those derived from the methods given.

A common-sense attitude towards precision and the additional technical labour which can improve precision seems to have been attained among chemists; why not among serologists? Perhaps because they feel they must be able to carry out the work themselves rather than seek the co-operation of colleagues better equipped or better trained in statistical techniques. A chemist could mention a laborious method needed only when the highest precision is aimed at, without such a vehement disavowal as that on page 214: "Even for those with the ability, the time, and the energy to use the method, it is probably not worth while to do so for samples of less than a thousand, or . . ." Could not these exceptional beings be allowed to judge for themselves? The whole passage is strangely irrational, and is reinforced by numerous asides throughout the chapter.

The basis for judging whether additional computational labour is "worth while" is surely the factual one of whether an equal increase in precision is obtained more cheaply (or more quickly) by doing more sums than by collecting more blood. It is, of course, usually found that refinements of statistical technique, in spite of all the rhetorical objections with which they are assailed, are by far the most economical method open to us.

No criticism, however, of what is, after all, not the author's main business, can disguise the fact that both Dr. Mourant and the Nuffield Blood-group Centre of the Royal Anthropological Society may congratulate themselves on a very fine job well done.

R. A. FISHER.

CHEMISTRY OF METABOLISM

Chemical Pathways of Metabolism. Edited by David M. Greenberg. Volume I. (Pp. 460+ix. $11.) New York: Academic Press Inc. London: Academic Books Ltd. 1954.

It is the purpose of this book to survey existing knowledge of the chemical steps in the metabolism of the major constituents of living organisms, each chapter having been written by an expert in a specialized field of research. The book, which is labelled Volume I, opens with an excellent chapter on "Free Energy and Metabolism," by A. B. Pardee, containing an illuminating discussion of the difference between free energy and heat, a matter that often vexes the non-specialist. Then follow chapters on "Enzymes in Metabolic Sequences" (O. E. Green), "Glycolysis" (P. F. Stumf), "Tricarboxylic Acid Cycle" (H. A. Krebs), "Other Pathways of Carbohydrate Metabolism" (S. S. Cohen), "Biosynthesis of Complex Saccharides" (W. Z. Hassid), "Fat Metabolism and Acetoacetate Formation" (I. L. Chaikoff and G. W. Brown), and "Sterol and Steroid Metabolism" (D. K. Fukushima and R. S. Rosenfeld). Much in the field of metabolism is thus left for a future volume or volumes, but no indication is given of when a succeeding volume will appear or of the topics to be discussed therein.

As is inevitable in a collaborative volume, the same standard is not maintained in each chapter, but on the whole the discussions are lucid and complete. The medical man may well ask where all this is leading with respect to medicine. A volume of this type certainly assists in the transformation of isolated, miscellaneous, and apparently unrelated facts into an orderly, coherent, and harmonious body of knowledge, and with Virgil we may say, "Happy is he who knows the causes of things." Over 250 years ago John Edwards wrote of chemistry: "This Spagyrick Art . . . hath had prodigious additions made to it lately. . . . Medicaments (consisting of Oyls, Spirits, Tinctures, Salts, ets.) are produced, and the Healthfulness of Men's bodies, and their Longevity are procured, and the Almighty Creator thereby Exalted and Honoured" (*A Compleat History of All Dispensations and Methods of Religion*, 1699). What chemistry was supposed to achieve for the eighteenth century biochemistry is surely bringing about in the twentieth, and the physician of the future will certainly not fail to find of practical significance much that is at present regarded by some as recondite or esoteric in the subject of biochemistry.

F. G. YOUNG.

SYNOPSIS OF OBSTETRICS AND GYNAECOLOGY

A Synopsis of Obstetrics and Gynaecology. By Aleck W. Bourne, M.A., M.B., B.Ch.(Camb.), F.R.C.S.(Eng.), F.R.C.O.G. Eleventh edition, fully revised. (Pp. 536+viii; 170 figures. 25s.) Bristol: John Wright and Sons, Ltd. 1954.

It is almost traditional for books written in note form for revision or cram purposes to be scorned by the theorists in education. Yet it is an attitude which is difficult to maintain without self-deception or dishonesty, especially while examinations remain the test of knowledge and the main objective of the sensible undergraduate. Lecturers may present their subjects in ways which satisfy the strictest standards of the experts on how to teach, but as an examination approaches the realistic student, who is an expert on how to learn, looks for memory aids which will enable him to marshal his factual knowledge quickly and at the right time. This plan is surely to be commended rather than despised, and is in fact used by most of us on all manner of occasions at all times in life. Some can manufacture their own tables, classifications, and mnemonics, others find it difficult or learn to do so only after benefiting from those prepared by a professional. Mr. Bourne is a professional, nay a veritable master, at sifting wheat from chaff, at simplifying complicated problems, and at emphasizing those points which are of importance both for the purposes of examinations and for subsequent practice. Moreover, within the limits of his objectives of conciseness and clarity he writes so well that the reader who has some previous knowledge of obstetrics and gynaecology, as all are expected to have, easily forgets that he is studying a "synopsis."

This new edition has been extensively revised and includes many of the latest views and developments which have a real chance of being widely accepted for a reasonable time to come. The small, simple diagrams do much to elaborate the text, while the index is unusually complete and stands up well to stringent testing. On the whole the theory is rather better than the practice, especially in the obstetrical section, but this is perhaps inevitable in a book of this kind. A not very important, although disturbing, finding is a unicornute uterus defined and illustrated as a "bicornute uterus with one horn underdeveloped."

The need for synopses and the popularity of this one are exemplified by the fact that it has been in demand and use for forty-one years. Moreover, Mr. Bourne has been responsible for it from the outset. It is almost incredible that he could have been old enough to have done so well with the first edition and yet have remained young enough to have written this modern and stimulating eleventh volume.

T. N. A. JEFFCOATE.

EMERGENCIES IN MEDICAL PRACTICE

Emergencies in Medical Practice. Edited by C. Allan Birch, M.D., F.R.C.P. Fourth edition. (Pp. 610+xii; illustrated. 32s. 6d.) London and Edinburgh: E. and S. Livingstone Ltd. 1954.

Six years after its first publication in 1948 this book now appears in its fourth edition, which contains much new material. It thoroughly deserves its apparent popularity, for it is a very good book indeed. The reviewer's cliché that "no doctor's library should be without it" is justified in this case, for there are few clinicians, in whatever specialty, who will not on occasion have reason to profit from the remarkable amount of sound, and at times unusual, information which the volume contains. Twenty-three well-known authorities contribute practical, explicit, and succinct articles of a type suitable for a doctor faced with an acutely ill patient or a critical situation. Discussions on diagnosis and principles of treatment are minimal, but sufficient to prevent the work from being uninteresting or degenerating into a mere list of tabulated therapeutics. The printing, diagrams, and illustrations are excellent and the price moderate.

Nearly all the usual acute non-surgical conditions are dealt with, and the word "emergency" has been liberally interpreted to include such conditions as acute urinary infections and pneumonia. In addition the book contains a great deal of singular, yet useful, information not otherwise readily available; information concerning, for example, emergencies in Roman Catholic mothers during pregnancy, emergency baptisms, medico-legal problems at sea, telephone numbers of emergency bed services, where to get antivenom for adder-bites, and so forth. The drugs mentioned in the text are usually in the official nomenclature, and their proprietary equivalents are given in an appendix; but this has not invariably been achieved successfully, and names like "seconal," "benadryl," and "nembutal" frequently appear. It is surprising that picrotoxin is still given pride of place over amphetamine in the treatment of barbiturate poisoning; that no instructions are given to administer potassium salts by mouth as a routine measure to all patients recovering from diabetic coma; and that delirium tremens is not specifically mentioned—it is usually a more common emergency for the practitioner to deal with than baptism. The index, of great importance in an emergency reference-book of this kind, is not quite up to the really first-class standard of the rest of the book.

D. M. DUNLOP.

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CARCINOMA OF THE BODY OF THE UTERUS

Only in recent years has an attempt been made in the mortality statistics of England and Wales to separate endometrial from cervical carcinoma. In the three years 1950–2 deaths in women from all malignant neoplasms numbered 125,361, of which 12,221 were uterine. Of all malignant neoplasms 6.2% were cervical, 2.8% endometrial, 0.08% "others including chorionepithelioma," and 0.6% "unspecified." The reliability of mortality statistics for uterine carcinoma is open to question, for even experienced histologists may be unable in some cases to distinguish between endometrial and cervical adenocarcinoma. However, there has certainly been a change in the incidence of the types of cancer prevalent in women since the beginning of this century. As Hoffman's collection of statistical data[1] shows, uterine carcinoma was the commonest form of cancer in women in the early part of the century, and in 1908–12 constituted 20% of all deaths due to malignant disease, when cancer of the breast accounted for 17%. In recent years the breast has accounted for 20% and the uterus for 12%, or less still latterly.

The estimates of the relative incidence of the three types of uterine carcinoma vary widely,[2] but it is probable that cervical is three times as common as endometrial and that cervical epidermoid is at least ten times as common as cervical adenocarcinoma. Corporeal carcinoma occurs some 8–10 years later in life than cervical. Cullen[3] found the maximum incidence to occur in the sixth decade of life; the figures of Norris and Vogt[4] showed an average age of 53.3 years and Speert's[5] series an average age of 56.6 years. Rarely does the disease occur before the age of 30 years, but, unlike cervical carcinoma, it is not uncommon after the age of 65 years. Nine of Willis's 31 patients were over this age. In Jewesses endometrial carcinoma is relatively more common than cervical carcinoma, since the latter form has a very low incidence in this race.[5,6] A matter of some interest here is the low incidence of penile carcinoma among Jews. Negroes apparently have a low incidence of corpus cancer and a high incidence of uterine myoma.[5] If the Hebrew race is left out of account, child-bearing is found to predispose to carcinoma of the cervix, while carcinoma of the corpus is more frequent in the nulliparous.[4,5,7]

In a recent article on the aetiology of corpus carcinoma Way[8] has reported a series of 153 cases and concluded that "there is some evidence to show that overactivity of the anterior pituitary may lead to many different manifestations including fibroids, diabetes or carcinoma of the corpus, either singly or in combination." The supposed association of diabetes with corpus carcinoma is probably not widely recognized in Britain, though there have been reports in the American literature quoted by Way,[8] Scheffey *et al.*,[9] Moss,[10] and Palmer *et al.*[11] As deduced from the glucose-tolerance test, Way found 29% of diabetics and 48% of pre-diabetics in his cancer series. Of 133 women without endometrial cancer who had ceased to menstruate after the age of 50 years—and who may be more liable to develop this disease—12% were found to be diabetic and 41% pre-diabetic. Five of these pre-diabetics subsequently developed diabetes. In a control group of 58 patients, 3% were diabetics and 30% pre-diabetic. This diabetes is of the insulin-resistant or pituitary type, more common in women than men, and with its greatest incidence in the fifth and sixth decades of life. In his cancer series and in a group of 88 diabetic women Way[8] found evidence of a late cessation of menstruation, the figures for the former group being comparable to those of Crossen and Hobbs.[12] Since Crossen and Hobbs first published their findings there have been many conflicting reports on this relation, and Speert[5] and Willis[2] state that there are no significant abnormalities of menstruation in these cases. Way's figures, however, seem significant, and it is unfortunate that no indication is given of the incidence of diabetes in the patients with cancer who ceased menstruating before the age of 50 and who appear to form at least 34% of the series.

[1] *The Mortality from Cancer throughout the World*, 1915, Newark, New Jersey.
[2] Willis, R. A., *Pathology of Tumours*, 1953, Butterworth, London.
[3] *Cancer of the Uterus*, 1900, Kimpton, London.
[4] *Amer. J. Obstet. Gynec.*, 1924, **7**, 550.
[5] *Cancer*, 1948, **1**, 584.
[6] Kennaway, E. L., *Brit. J. Cancer*, 1948, **2**, 177.
[7] Lane-Claypon, J. E., and McCullagh, W. M. H., *Min. of Health Rep. Pub. Health Med. Subj.*, 1927, No. 47, London.
[8] *J. Obstet. Gynaec. Brit. Emp.*, 1954, **61**, 46.
[9] *Amer. J. Obstet. Gynec.*, 1946, **52**, 529.
[10] *Amer. J. Roentgenol.*, 1947, **58**, 203.
[11] *Amer. J. Obstet. Gynec.*, 1949, **58**, 457.
[12] *J. Mo. med. Ass.*, 1935, **32**, 361.
[13] In J. H. Teacher's *Manual of Obstetrical and Gynaecological Pathology*, 1935, Oxford Univ. Press, p. 202.
[14] Lipschutz, A., *Steroid Hormones and Tumours*, 1950, Williams & Wilkins, Baltimore.
[15] *Proc. Amer. Ass. Cancer Res. (Abstracts)*, 1954, **1**, No. 2, 47.
[16] *Cancer*, 1952, **5**, 215.
[17] *J. Obstet. Gynaec. Brit. Emp.*, 1950, **57**, 737.
[18] *Gynaecologic and Obstetric Pathology*, 1952. W. B. Saunders, Philadelphia and London.
[19] Proc. Internat. Congress of Genetics, Bellagio, 1953.
[20] Warthin, A. S., *J. Cancer Res.*, 1925, **9**, 279.
[21] Hauser, I. J., and Weller, C. V., *Amer. J. Cancer*, 1936, **27**, 434.
[22] Himsworth, H. P., *Lancet*, 1949, **1**, 465.

Whether or not there is an association between uterine myomas and endometrial carcinoma would seem to depend largely on the accepted incidence of the former among the general population. The figures for most reported series reviewed by Speert[5] vary from 35 to 38%. In 200 consecutive necropsies in women over 40 years of age Speert found an incidence of 36.5% and concludes that there is no evidence to support any special association between these two tumours. Way states that the incidence of myomas in gynaecological practice is far less than 30% and considers the incidence of 34% in his series to be significant. Stewart[13] in a series of 2,550 necropsies at the Leeds Infirmary in women over the age of 20 years found 17.5% of uterine myomas, a figure which supports Way's statement.

Fibromas and myomas have been induced with oestrogens in guinea-pigs,[14] though these tumours have not been confined to the uterus, and it is doubtful if they are the true counterpart of the human tumours. Stimmel[15] has produced evidence which suggests that the guinea-pig's mechanism for oestrogen inactivation is of a lower order than that of rats and mice, and this limited capacity may partly explain the relative ease with which fibroid tumours are induced in the guinea-pig. Excessive and prolonged action of oestrogens has been held responsible for the relation between feminizing tumours of the ovary, endometrial hyperplasia, and endometrial carcinoma. Diddle,[16] reviewing the literature on feminizing tumours of the ovary, found 73 endometrial and five cervical carcinomas among 1,195 published reports. He also found that endometrial carcinoma was four times more common with thecomas than with granulosa-cell tumours: 40% of the cases were also associated with uterine fibromyoma or hypertrophy, the former being more commonly associated with theca- than granulosa-cell tumour. Haines and Jackson,[17] analysing 40 cases of granulosa-cell tumours, found no instance of endometrial carcinoma, though 60% of their cases were in the fifth and sixth decades. The endometrial pattern was recorded in only nine cases, and seven of these showed an oestrogenic pattern. It is the postmenopausal hyperplasia which may lead on to malignancy, and, as Novak[18] states, there is no sharp histological distinction between some hyperplasias and carcinoma, and sometimes the two conditions may co-exist. These findings are analogous to those of other organs under endocrine control—for example, breast and prostate.

Speert[5] in his 225 cases of corpus cancer found eight breast tumours, of which six were malignant. It has now been conclusively demonstrated that the ovaries, because of their share in oestrogen production, are largely but not entirely responsible for the induction of breast cancer, and Muhlbock[19] has recently demonstrated the possibility of a pituitary gonadotrophin playing a part in the induction of breast cancer. There is some evidence, though not conclusive, indicating a hereditary factor in the aetiology of corpus cancer.[20 21] There is a more definite family history in diabetes mellitus, most clinics finding such a history in 30% of adults and 52% of children.[22] The apparent association of diabetes mellitus of the anterior pituitary type with corpus carcinoma, shown for the first time in Britain by Way, should call for further investigations along similar lines in clinics for gynaecology and diabetes to establish or disprove its existence. If the general incidence is as high as Way has found in his series, it seems remarkable that the association has not been reported here before.

PAY-BEDS

The recent declaration at Scarborough of the Labour Party's policy to abolish pay-beds in hospitals if they succeed at the polls in the next general election is but another example of the flexibility of the political conscience. Six years ago Mr. Bevan appeared to be only too delighted to offer the consultant world the freedom of private beds in hospitals, even some without "price ceilings." Those who took his words at face value had forgotten his indiscreet remark in the House of Commons about the dropping of ripe fruit. In spite of the Amending Act of December, 1949, Labour spokesmen have not ceased to clamour for a whole-time salaried State medical service, and the attack on private beds is plainly directed to this end. It is interesting to notice that no Labour voice is heard to protest when distinguished Labour politicians "jump the queue" by being treated in the private wards of hospitals or well-known clinics. They need privacy because often they have to conduct business from a sick-bed. Delay in treatment, which from a medical standpoint may well be unimportant, may be a grave disadvantage to a man with heavy obligations. A Cabinet Minister, we suggest, has a right to jump the queue. It would, of course, be highly dangerous to admit this, because to do so would be to admit that there are priorities, that some men are less equal than others, and that "fair shares for all" as a slogan conceals within itself a number of awkward and insincere attitudes. There is no evidence that anyone in this country fails to get immediate treatment for urgent medical and surgical conditions, nor, for that matter, did they before July, 1948. There are delays in getting free hospital treatment for "cold surgery"—for

tonsillectomy and herniotomy, for example. These delays would certainly not be overcome by abolishing private pay-beds in hospital. They could be lessened by better organization. But the solution to the problem certainly does not lie in abolishing pay-beds. To attempt to do so ignores the wish of an increasing number of Britons to pay for the privacy and convenience—which Labour politicians seem to desire as strongly as anyone else—of treatment by consultants and specialists of their choice. The growing number of those subscribing to provident schemes bears witness to this. And surely this is a healthy and desirable move. The more people are willing, at financial sacrifice to themselves, to provide privately against the risk of disease requiring institutional treatment, the less will be the burden falling upon the State, with the consequent freeing of State funds for hospital extension. It should be in the interest of the State to foster any move to independence of itself in seeking private general and specialist treatment. Apart from anything else, the success of such moves would help the State to conceal from the electorate its inability to establish a medical Utopia upon earth.

"HORROR COMICS"

Probably few medical men have seen what by a strange abuse of language are called "comics," and may believe that they are just exaggerated versions of the relatively innocent "penny dreadfuls" of their youth. One look at them has been enough to convince the new Home Secretary, Mr. Lloyd George, that some action is necessary—action, it is hoped, that will be speedy and effective to prevent the sale of a foul kind of literature calculated to violate the immature mind. No family doctor, and none of those who take part in the many services directed to bringing up the young as decent citizens, can remain indifferent to these attempts to present to the minds of readers scenes of horror, terror, and unbridled violence. Some of the advertisements in these magazines, however, suggest that they are aimed more at the raw and callow youth from whom the "Teddy boys" are recruited, and would seem more calculated to pervert their mentality than the exploitation of frankly sexual themes. It appears that the printing matrices of these magazines are exported from the United States, and the "comics" are then reproduced in England, Scotland, and many of them, it is odd to note, in the Republic of Ireland, where some kind of censorship of publications is in force. During the past year we have witnessed the Puritan conscience at work in its effort to ban the *Decameron*. This somewhat wayward manifestation should not, however, blind the observer to the fact that there exists a pornographic literature that deliberately exploits the sexual instinct to its debasement. The "horror comics," the subject of review elsewhere in this issue, are no less obscene than pornography if we accept the following definitions of obscene given in the *Oxford English Dictionary*: "disgusting, repulsive, filthy, foul, abominable, loathsome." The Home Secretary will be supported by responsible public opinion in any action he takes to bring to an end this abominable misuse of wood-pulp.

EFFECT OF COBALT ON ERYTHROPOIESIS

The part played by the cobalt-containing vitamin B_{12} in erythropoiesis is generally known. In the absence of available vitamin B_{12}, as in pernicious anaemia, the maturation of red cells is retarded and a macrocytic, hyperchromic anaemia develops. Specific actions of cobalt on the bone marrow are less well understood. It was pointed out by Filmer[1] in 1933 that one of the manifestations of cobalt deficiency in sheep is a normocytic, normochromic anaemia. This observation has been repeatedly confirmed, and shown to occur in several animal species.[2,3] The anaemia is cured by giving very small quantities of cobalt salts. Parenteral administration of cobalt appears to be much less satisfactory than oral administration, which indicates that the beneficial effect is at least partly exerted through stimulation of growth of the ruminant and intestinal flora.[4] Conversely, excess cobalt given to animals stimulates the production of red cells to such an extent that polycythaemia ensues.[5] This finding has also been confirmed by many workers using different animals. The mechanism by which cobalt produces polycythaemia is obscure, the more so since the effect is said to be reversed by such diverse substances as liver extract, choline, adequate dietary sulphur-containing amino-acids, and ascorbic acid.[6–8] In experimental animals in which inflammation has been produced by turpentine injections the formation of red cells is often diminished. The development of anaemia in such animals can be counteracted by simultaneous administration of cobalt.[9]

There is scattered evidence to suggest that the results of these experiments are applicable to the human subject. Berk *et al.*[10] report that eight patients without

[1] *Aust. Vet. J.*, 1933, **9**, 163.
[2] Neal, D. M., and Ahmann, C. F., *J. Dairy Sci.*, 1937, **20**, 741.
[3] Frost, D. V., and Elvehjem, C. A., *J. biol. Chem.*, 1939, **128**, xxxi.
[4] McCance, R. A., and Widdowson, E. M., *Ann. Rev. Biochem.*, 1944, **13**, 315.
[5] Waltner, K., and Waltner, K., *Klin. Wschr.*, 1929, **8**, 313.
[6] Davis, J. E., and Allison, M. J. C., *Proc. Soc. exp. Biol. (N.Y.)*, 1943, **54**, 266.
[7] Griffith, W. H., *et al.*, *J. Nutr.*, 1942, **23**, 603.
[8] Barron, A. G., and Barron, E. S. G., *Proc. Soc. exp. Biol. (N.Y.)*, 1936, **35**, 407.
[9] Gubler, C. J., *et al.*, *J. biol. Chem.*, 1950, **184**, 575.
[10] *New Engl. J. Med.*, 1949, **240**, 754.
[11] Ibid., 1949, **240**, 749.
[12] *J. Lab. clin. Med.*, 1951, **37**, 182.
[13] Ibid., 1953, **41**, 56.
[14] Baxter, C. R., *British Medical Journal*, 1939, **1**, 534.
[15] Waltner, K., *Acta Paediat. (Uppsala)*, 1930, **11**, 438.
[16] *Klin. Wschr.*, 1951, **29**, 80.
[17] *J. Nutr.*, 1941, **21**, 93.
[18] Kato, K., *J. Pediat.*, 1937, **11**, 385.
[19] Caussade, L., *et al.*, *Arch. franç. pédiat.*, 1947, **4**, 293.
[20] *Arch. Dis. Childh.*, 1954, **29**, 85.
[21] Dorrance, S. S., *et al.*, *Amer. J. Physiol.*, 1943, **139**, 399.
[22] Mackay H. M. M., *Arch. Dis. Childh.*, 1933, **8**, 145.

anaemia who received 200 mg. cobaltous chloride daily all showed a reticulocytosis and a moderate increase in haemoglobin, red cells, and haematocrit readings. There is no evidence, however, that an abnormal cobalt metabolism is responsible for polycythaemia vera. In view of the successful response to cobalt of the anaemia of inflammation in animals, it is of interest that the anaemia in five human cases of chronic sepsis treated by the same authors showed a significant improvement. Robinson *et al.*[11] treated nine anaemic patients with chronic osteomyelitis or soft-tissue suppuration with cobalt and stated that in all cases a return to normal blood values occurred. Shen and Homburger[12] reported beneficial results from cobalt administration in nine out of sixteen cases of anaemia associated with advanced cancer. Gardner[13] treated seventeen anaemic patients suffering from chronic renal disease for four weeks or longer with cobaltous chloride, and reported significantly increased erythropoiesis in all during the period of treatment. Toxic effects—anorexia, nausea, vomiting, and urticaria—are relatively common with high dosages of cobalt; the possibility of renal damage in man has not yet been excluded. Cobalt is poorly tolerated and produces little or no effect in pernicious anaemia[10] and simple iron-deficiency anaemia.[14 15] Weissbecher[16] has developed a cobalt-amino-acid complex for parenteral administration which is said to ensure a constant, slow release of cobalt in the tissues and to avoid gastro-intestinal irritation. This preparation may be useful clinically. Frost *et al.*[17] have pointed out that milk contains only very small amounts of cobalt, and it might therefore be expected that infants would be more liable to cobalt deficiency than adults. In anaemic infants cobalt sometimes potentiates the beneficial response which often occurs after iron administration.[15 18 19]

Coles and James[20] have recently investigated the effect of cobalt and iron supplementation on the anaemia which develops as a rather common complication of prematurity. They report that administration of 10 mg. of cobalt sulphate daily for the first ten days of life is of value in preventing the early development of anaemia. With continued iron and cobalt supplementation the incidence of hypochromic anaemia (long recognized as a risk in prematurity) was reduced. Toxic effects were not encountered in the dosages used, and weight gain was not impaired, as it sometimes is in animals receiving cobalt.[21]

In several of the studies quoted the techniques used and the mode of assessment of results are not entirely above criticism. Thus, the possible effects of cobalt administration on the blood volume have not always been taken into account. Nevertheless, the results suggest that cobalt has a stimulant effect on erythropoiesis in man. Polycythaemia induced by cobalt has been shown to improve the working performance of anoxic rats, but the performance of the animals was at its best after the cobalt treatment was discontinued and before the polycythaemia subsided.[21] Those who have used cobalt on anaemic patients claim that the symptoms are at least partly relieved by treatment. Full and carefully controlled investigations of the effects of cobalt on the anaemias of sepsis, chronic nephritis, and infancy are needed. On the available evidence it seems that small supplements of cobalt and also of copper[22] should be given together with iron to anaemic premature infants, and that cobalt administration is worth a trial in the anaemias of chronic sepsis, renal insufficiency, and carcinomatosis.

CHILDREN'S RECEPTION CENTRES

In 1820 John Falke, in his efforts to find homes for vagrant children,[1] learnt that it was necessary to provide a period of "settling in" and of preliminary training before the children could be passed on, and for this purpose he took over a country house which must have been one of the first reception centres. Dr. C. P. Blacker,[2] in his plan for the organization of mental health services, recommended that "in each area of a million, there should be established . . . a children's reception centre to which could be sent, through the channels of any responsible agency, children who, for any reason whatsoever, have to be found a home." In the same year, 1946, the Curtis Committee also recommended "that in the area of each responsible authority there should be at least one reception home" where medical and psychological advice should be available. Dr. Hilda Lewis has now published a full account[3] of such an experimental home established at Mersham, in Kent, between October, 1947, and July, 1950. The venture, which was made possible through the generosity of the Nuffield Foundation, was fortunate in having Dr. Blacker as chairman of its advisory committee, and in its association with Miss Leila Rendel of the neighbouring Caldecott Community.

This experiment is of particular value in view of the sharply conflicting opinions expressed by various authorities on the benefits and even the dangers of such centres. In an admirably balanced weighing of the pros and cons, Dr. Lewis concludes that the experience and evidence "accumulated at the Mersham Centre compel the firm conviction that reception centres, though not ideal, are indispensable at the present time for dealing with a large proportion of deprived children." She modifies the rather sweeping recommendations of the Curtis Committee in several ways; in particular she recommends that the social, psychological, and medical examination of the child should be carried out at home if at all possible and that "children under 5 should not normally be taken into a reception centre unless they are members of a family which must be kept together, or unless they present psychiatric troubles calling for close study." On the other hand, Dr. John Bowlby,[4] one of those who had formerly expressed most concern about reception centres, now concedes that "some of us have overstated the case against them." Further, Dr. Lewis through her follow-up study is able to show that there may not be full justification for the very pessimistic views of such workers as Bender, Lowrey, Goldfarb,

[1] Wines, E. C., *The State of Prisons and of Child-Saving Institutions*, 1880, Cambridge.
[2] *Neurosis and the Mental Health Services*, 1946, London.
[3] *Deprived Children*, 1954, London.
[4] *The Times*, October 15, 1954.
[5] Cmd. 9145, 1954, H.M.S.O., London.

and Bowlby, on the effect of separation of a child from its mother in the early years. She concludes:

"Nearly a third of the children who were separated from their mothers (before the age of 5) were, however, in a satisfactory condition at the end of the follow-up period, and a permanent separation before the age of 2 had not been the prelude to a particularly unsatisfactory condition of the child at the end of the period."

Dr. Lewis's book may be advantageously read in conjunction with a recent Home Office publication[5] which states that the number of children which came "into care" in England and Wales during the twelve months to November 30, 1953, was 39,300. Of this large number, 23,361 were accepted because of the infirmity, temporary illness, or absence, of parent or guardian; no doubt a large proportion of the remaining 15,939 children had need of the sort of services provided by reception centres. The Children's Act of 1948 lays a duty upon all county and county borough councils to provide a reception centre for these children, and they will have in Dr. Lewis's book a valuable blueprint upon which to base their plans.

DISSEMINATED SCLEROSIS IN NORTHERN IRELAND

A recent survey of disseminated sclerosis in Northern Ireland carried out by Allison and Millar[1] is noteworthy for the fact that all reported cases were personally examined by one or other of the authors, either in Belfast or during country visits. Over a three-year period, 1948–51, 887 cases were notified, of which 187 were discarded. On the basis of history and clinical findings the remaining 700 cases were classified as follows: early 79, probable 476, and possible 145.

The 1951 census in Northern Ireland showed a population of 1,370,709. From this the authors were able to arrive at a prevalence rate of this disease of 79 per 100,000 after excluding persons under the age of 20. This figure suggests that in Northern Ireland one case of disseminated sclerosis may be found for every twelve to thirteen hundred of the adult population. In an attempt to determine the age of onset, Allison and Millar selected a period, 1937–1951, and confined their observations to the 411 patients whom the disease had first attacked in that time. They were able to estimate the average annual number of onsets of the disease in 100,000 persons in each age and sex group. Their figures show that the risk of contracting the disease is greatest at ages 30–39, and is more than twice as great at ages 40–49 as at ages 10–19 years. In three recent series[2–4] covering 1,582 cases, the disease began below the age of 20 in 253 (16%), and over the age of 40 in 184 (12%). The Northern Ireland figures, therefore, would appear to indicate a shift of incidence of the disease in that country towards the higher age groups. By determining the geographical distribution by place of onset, Allison and Millar found that the disease in Northern Ireland does not affect rural populations more than urban, nor did they find any evidence to suggest a focal incidence.

Millar and Allison, in the same report, confirmed previous findings[5–7] that disseminated sclerosis has a significant familial incidence. Their figure of 6.58% closely corresponds with that of the Middlesex Hospital series—namely, 6.5%. These authors are the first to compare the expected risk in sibs of patients with disseminated sclerosis with the rate in a control population studied in the same area and at the same time. They found the risk to be approximately ten times greater in sibs of patients than in the control population, and agree with the view of Compston, Pratt, and McAlpine[6] that the excess risk is not due to common environment or to infection, but rests on a genetically determined predisposition. The methods used in the planning and execution of this survey set a standard by which all future studies in this field will be judged.

[1] Allison, R. S., and Millar, J. H. D., *Ulster med. J.*, 1954, **23**, *supplement* 2, 5.
[2] Müller, R., *Acta med. scand., supplement* 222, 1949.
[3] Adams, D. K., *et al.*, *British Medical Journal*, 1950, **2**, 431.
[4] McAlpine, D., and Compston, N., *Quart. J. Med.*, 1952, **21**, 135.
[5] Curtius, F., *Multiple Sklerose und Erbanlage*, 1933, Leipzig.
[6] Pratt, R. T. C., *et al.*, *Brain*, 1951, **74**, 191.
[7] Pratt, R. T. C., *Ann. Eugen. (Camb.)*, 1951, **16**, 45.

TREATMENT OF LEG ULCERS

For more than two thousand years doctors have been writing about the treatment of leg ulcers, but so remarkable has been the progress of medicine during the last fifty years that little notice is now taken of any but recent medical publications. This short-sightedness is similar to that described by Benjamin Bell,[1] who wrote in 1789: "Since the commencement of the present century very considerable improvements have been made both in Medicine and in Surgery. The latter particularly, during the course of this period, seems to have been enriched with more real knowledge than it was ever before possessed of. From this consideration, it may possibly be alledged by some, that nothing new can now be offered on the subject of Surgery; and therefore, that any farther publication in that line must, in some measure, be superfluous." Sir John Erichsen[2] took a similar view in 1873 when he said: "We have carried the art of surgery to the highest degree of perfection of which as an art it is susceptible." Lord Moynihan in the 1930s expressed much the same opinion.

The study of history provides a corrective to this unfortunate attitude of mind, for the historical approach gives a reasonable perspective, and, as Sir Winston Churchill has said, "The longer we look back the further we can look forward." It is, for example,

[1] *A treatise on the theory and management of ulcers.* Edinburgh.
[2] *British Medical Journal*, **2**, 414.
[3] *La grande chirurgie de Guy de Chauliac.* 1890, Paris.
[4] *Chirurgia: de chirurgia scriptores optimi.* Zurich.
[5] *A new method of treating old ulcers of the legs.* 2nd ed., Bristol.
[6] *Lectures illustrative of various subjects in pathology and surgery.* London.
[7] *Of Medicine in eight books.* 1756, London.
[8] *Med. Obs. Inqu.*, 1771, **4**, 347.
[9] Irving, L. M., and Tolmach, J. A., *J. Amer. med. Ass.*, 1954, **156**, 1219.
[10] *Lectures on the cause and treatment of ulcers of the lower extremity.* London.
[11] *Lancet*, **1**, 859.
[12] *Surg. Gynec. Obstet.*, **98**, 667.
[13] *Severall chirurgicall treatises.* London.
[14] *A treatise upon ulcers of the legs.* London.
[15] *British Medical Journal*, **2**, 624.
[16] Ibid., **2**, 996.
[17] *Angiology*, **3**, 335.

salutary for our sense of proportion to remember that the diachylon bandage has been introduced on several occasions and heralded as an important advance—by Guy de Chauliac[3] in 1363, by Marianus Sanctus Barolitanus[4] in 1555, by Thomas Baynton[5] in 1799, by Sir Benjamin Brodie[6] in 1846, and again in recent years. The blunt hook of Celsus[7] has been replaced by the vein stripper, and in place of the wine applied to ulcers by Galen we use other antiseptics. Else[8] placed lead plates over ulcers, and now silver foil is being used.[9] Critchett in 1849[10] covered ulcers with the lining membrane of egg-shells and Troensegaard-Hansen in 1950[11] used amnion. The eighteenth-century surgeon cleaned the ulcer of slough by a digestive application, and Spier and Clifften in 1954[12] use plasminogen and streptokinase. The principles of treatment have altered little. The common factor in the successful management of leg ulcers by a variety of methods used since early times has remained firm compression of the leg from toes to knee. Celsus[7] applied a linen roller, and Paré also bandaged the leg firmly. Wiseman in 1676[13] introduced the laced leather stocking, Underwood in 1783[14] the "Welch flannel" bandage, Martin in 1878[15] one of india-rubber, and Dickson Wright in 1930[16] the elastic plaster bandage. It is significant that most surgeons insist that a leg should have elastic support after operative treatment for ulceration.

Recently Spier and Clifften[12] have described the results of treatment of a small series of patients with chronic leg ulcers by the local application of hyaluronidase, plasminogen, and antibiotics. The sixteen patients had been unsuccessfully treated for some time previously by routine methods, which are not specified. Plasminogen and streptokinase were employed to clean the ulcer and terramycin and hyaluronidase applied to penetrate into the surrounding infected tissues. The ulcers of nine patients were healed in from one to thirteen weeks and the remainder were improved. All wore elastic bandages. One patient became sensitive to terramycin. It is difficult to assess the part played by hyaluronidase in this series and it would be interesting to determine whether the results are inferior when terramycin is used alone. Popkin[17] claimed good results in the treatment of chronic ulceration by hyaluronidase introduced by iontophoresis, though it has disappointed other workers. Nevertheless, Spier and Clifften's methods seem worth repeating, preferably with bacteriological control, since terramycin may not be the most suitable antibiotic for every infected ulcer. Local applications thought to promote tissue growth and healing have long been used in the treatment of leg ulcers; powdered red blood cells have been tried for this purpose. Recently Milberg and Tolmach[9] have reported good results from packing ulcers with absorbable gelatin sponge powder together with the application of elastic bandages. In 86 patients of 106 treated in this way ulceration was healed and the results were better than with other methods. The history of the treatment of leg ulcers contains many reports of new methods hailed at first as great advances but doomed after a time to oblivion. Nevertheless, fresh lines of treatment are being devised, even though they are based on old principles.

NOBEL PRIZE FOR MEDICINE

It was announced in Stockholm last week that the 1954 Nobel Prize for physiology and medicine had been awarded to Professor John F. Enders, Boston, Professor Frederick C. Robbins, Cleveland, and Professor Thomas H. Weller, Boston, jointly for their discovery of the ability of the poliomyelitis virus to grow in cultures of different tissues. This award of the highest honour in international science to these three leading experts in preventive medicine will be welcomed by the medical profession throughout the world and not least by their many friends in Britain, some of whom have had the good fortune to experience the hospitality of the Children's Medical Center in Boston. The honour is a great tribute to the staff of this famous institution.

Dr. John F. Enders, associate professor of immunology at Harvard Medical School and director of the research division, has spent a lifetime in the study of infectious disease, making many and varied contributions to the advancement of paediatrics before the achievement for which he now shares this honour with his two colleagues. Dr. Thomas H. Weller, professor of tropical health and assistant to Dr. Enders, is already at the age of 39 a leading authority on virus infections. Dr. Frederick C. Robbins joined the staff of the Children's Hospital in Boston after an outstanding career in the 1939–45 war, when he worked with Smadel on rickettsial infection. Now at the age of 38 he holds the post of professor of paediatrics in Cleveland. It is indeed a sound arrangement whereby in Boston and in other American universities research into infectious disease is closely associated with paediatrics.

A short article in 1949[1] referred to the successful cultivation of poliomyelitis virus in tissue culture of human embryonic skin and muscle. As has happened in the past in scientific research, chance played a part, for these cultures were being used for work with varicella virus; fortunately a few surplus tubes were inoculated with the Lansing strain of poliomyelitis virus. The significance of the finding that the virus would grow in nervous and non-nervous tissue was twofold. It brought to a close the era when poliomyelitis research was wholly dependent on monkeys, and it gave practical expression to the idea winning support at the time that poliomyelitis virus was not such a strict neurotropic agent as had hitherto been imagined. The way to immunization was being opened up. At last a practicable method was available for producing virus in large quantities for use in a vaccine and also for the detailed investigation of the disease process. The recognition that poliomyelitis viruses could be grown in tissue culture of different tissues is the most outstanding achievement since research into poliomyelitis began, and less than five years after the original report large-scale immunization has been tried out.

The next session of the General Medical Council will open on Tuesday, November 23, at 2 p.m., when the President, Sir David Campbell, will take the chair and will deliver an address.

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[1] *Science*, 1949, **109**, 85.

HORROR COMICS

"You didn't think we'd ever have the *real* Santa Claus in *this* horror mag, did you?" And thus an old witch draws to a close her tale of horror set out in a strip cartoon in lurid colour over seven pages. "I suppose you've been wondering just what I've got in this sack," she goes on. "It's only what's left of Carol's Mommy after that maniac was *through* with her."

The story began with Mommy having murdered her husband with a poker blow on the head. After tucking young Carol (aged about 8) into bed, Mommy (a handsome blonde) goes downstairs and turns on the wireless. A news item tells her that a homicidal maniac has escaped from a hospital for the insane, and, having "*brutally murdered four women*," is making for the village where she lives. He is wearing a Santa Claus costume. Then through four pages and 27 pictures Mommy registers horror, terror, and despair as she hears the maniac's knock at the door, sees his eye at a window, realizes she cannot call the police because of her husband's corpse in the house, tries to hide it, boards up windows—and then finds Carol's bed empty. She rushes downstairs to see Carol opening the front door and leading into the hall a leering, maniacal "Santa Claus." The witch then takes over to deliver her little colophon, and wishes her readers a "*Merry Christmas.*" (All italics are in the original.) The self-styled "comic" from which this story is taken bears March as its date, but a sense of reality is not one of the distinguishing marks of this brand of literature.

A typical so-called comic specializing in horror stories contains about half a dozen in that genre—and virtually to the exclusion of all else. Horror piles on horror; just occasionally the merely weird is left to stand in dim contrast to the homicidal clatter that fills the pages; but the ordinary run of stories, almost without exception in some of the comics, are concerned with violent, painful, brutal death. Frankly sexual themes hardly appear at all in these labyrinths of destruction, and the introduction of a sex maniac, as in the story quoted above, must be counted as sailing rather close to the wind—the wind, that is, in which Boccaccio's *Decameron* is held to be pornographic and these comics to be permissible.

Tortured Prisoners

Dungeons and torture are among the more realistic horrors of this strange world. In another comic, for instance, the story is told—and vividly illustrated over six pages of coloured pictures—of a gaoler (named Cochon) who starves his prisoners while tempting them with delicious morsels. At last one of them, a youth, tries to seize a roast pheasant leg, for which he is punished by a flogging from the gaoler. This punishment is depicted in a specially large illustration covering two-thirds of the page, and headed with the caption: "And for nearly thirty minutes the dungeon rang with the agonized screams of the young boy as Cochon brought the whip down brutally on his bleeding back again and again. . . ." The prisoners ultimately capture Cochon (one of them offers to "sell herself" to him while another bashes him on the head), and then eat him. He proves to be poisonous, however, and they are all found dead the next morning.

In striking contrast the same comic contains a half-page advertisement headed, "With God all things are possible." All sorts of problems can be solved . . . "*Money* or *Job Troubles? Love* or *Family Troubles?* . . ." "Is someone dear to you *Drinking* too Much? . . . " "Just clip this *Message* now. . . . WE will rush this wonderful *NEW Message of PRAYER and FAITH* to you by *AIR MAIL.*" The constant reader might well need something like that after a time.

Flights of bizarre and even insane fantasy are the stock-in-trade of these authors and artists—as they may be called for want of more appropriate terms. Opening an old book, the hero of one story reads: "The torture chamber is lit by torches that glisten on the agony and sweat of the dying victims . . . " "The walls are damp with mouldy moisture mingling with the rusty blotches left by former victims . . ." And so on. The father of this young man has constructed a Wellsian time-machine (for he is a "great scientist") and puts it at the disposal of his son, who wants to study history at first hand ("I wanted to be great too, in my own line as a writer"). Off he goes, the budding historian, into pre-history, battling with apes in numerous postures of alternating terror and attack. He ends up as a primeval ape himself. The reader feels in familiar company when he finds in another comic a whole-page advertisement offering ("free!") a collection of ten stamps each bearing Hitler's portrait.

Not for the Squeamish

Murdering his companion in the desert in order to drink his water, sprawling pitifully from mirage to mirage, the hero of another tale finally dies exhausted of thirst. Such are the simple elements of many of these stories—a brutish life, a violent death. Fancy is a little more playful in the next story to this one. Fiends on a distant asteroid mill about in their gruesome existence and speculate on the heaven to which death may release them. Finally the reader is addressed: "How do you feel in America, where each day you're living in Heaven?" Passing over a tale of torture by molten lead, the reader then comes upon one of the few manifestations in these magazines that life also has a beginning: a woman dug out of her grave gives birth to a baby. However, we return to form again at the end, the climaxes of the last three stories being, respectively, death in a machine for chopping meat, death by dissection for embalmment, and death at the jaws of a crocodile. No wonder this album, as it calls itself, is headed "Not for the squeamish," or that the editors of it in an introductory letter refer, perhaps ironically, to "this new polluted publication."

The language in which these characters give utterance to their doomed lives is naturally of the simplest. Sometimes nothing but shrieks, grunts, groans, and wails issue from their mouths in streams of vowels. Eeeah! Aie! Screeemm! Aaagh! Punctuation throughout the strip cartoons is on a system peculiar to them: commas, colons, semi-colons, and full-stops are not much seen. Three or more points . . . often do duty for all these, and the sentence usually ends with ! or, if a question, with ? For example: "Gone, she's gone! That crazy monster has her . . . He's bringing her to me as the final corpse I needed!" (A Frankenstein monster who kills people and takes their bodies for a doctor to experiment with is now bringing the corpse of the doctor's wife.) Seven-year-olds of any age would be able to follow the cartoons without serious difficulty, and the occasional stories mingled with them, though the punctuation is less hectic, would be as readily comprehensible. "Then the last thing he saw," one of them ends, "was its hideous, slavering jaws opening wide—for him." Or: "It was her uncle Mose Spoffard who for years had made a business of digging up and marketing the corpses which he had buried." The elementary appeal of the language is matched by the odd feature that none of the pages are numbered in these magazines, even when a table of contents appears. Perhaps such an orderly device as pagination might be thought out of keeping.

Most, but not all, of the horror comics are American in origin; some are marked "British Edition," though the only obviously British feature of these is the advertisements. Body-building devices and books are their principal wares, accompanied by pictures of taut muscles and mighty chests. They are on sale at many perfectly respectable bookshops and newsagents, though possibly not in the best-class establishments, and there is no hindrance, legal or other, to buying them. Most of them sell for 1s.; a few are rather more expensive; and the customer can put down his money without feeling bashful. There is nothing furtive in their sale—only, perhaps, in their perusal.

DOMICILIARY PSYCHIATRY

THE AMSTERDAM EXPERIMENT

Dr. A. QUERIDO, professor of social medicine at Amsterdam University, came over last week from Holland to speak at a public meeting at the Senate House of London University on the "Amsterdam Experiment." This is a system of dealing with the city's mentally sick which, beginning nearly 25 years ago as a plain economy measure, has become one of the most fruitful joint enterprises of social and psychiatric medicine. By the skilful use of a small central psychiatric staff it has proved possible to treat a great number of Amsterdam's mental patients in their own homes, where before they would have encumbered mental hospital beds. Apart from the therapeutic benefit to the patients in being kept in society, the Amsterdam scheme has resulted in a spectacular decline in the cost of the city's mental health services. Whether conditions in Britain are the same as in Amsterdam is debatable, but the interest of the Dutch methods and results to us in Britain, with our own vast mental hospital population, is obvious.

Professor Querido is the founder and chief architect of the Amsterdam experiment. His lecture was arranged by the National Association for Mental Health.

Background and Beginnings

Amsterdam, with her population of nearly 900,000, had a long tradition of independence and experiment in local government, said Professor Querido, dating from the days of the sixteenth and seventeenth centuries, when she was the commercial centre of the world, when she sent out her own ambassadors, and when she made war or peace at her own discretion. That tradition provided the soil in which the "Experiment" had grown.

In 1930, when the economic depression hit Holland, he had been appointed city psychiatrist, with a brief to cut the mounting cost of the care of the insane. There were at that time 300 clinical beds available for mental patients in the Amsterdam hospitals, but in addition there were 3,000 mental patients accommodated in institutions outside the city. An immediate survey showed that 10% of these patients, though admittedly mentally ill, did not really need to be in hospital; a home could be found for them, and a relative was ready and able to take care of them. That was the beginning. Soon it became evident that the criterion of whether a patient should remain in hospital was not whether he was suffering from a mental disease—that *in itself* was not enough—but whether the consequences of his disease made it impossible for him to live in society. The provision of even quite simple material aid would not infrequently turn the scale in favour of staying in society.

The next stage was the realization that the best way of reducing the numbers in the mental hospitals was not by discharging existing patients, but by preventing the admission of new ones. Demands for admission came from three sources: general practitioners, the police, and a few from the patient's family. A regulation was introduced to make it compulsory for all admissions, whether voluntary or by certification, to pass first through the hands of the city psychiatrist. Parallel with this, a 24-hour service was set up at the city psychiatrist's so that every case was promptly investigated *on the spot*, before being sent to clinic or hospital. The contrast between this and interviewing the patient for the first time in hospital could not be exaggerated: it made it possible to observe the whole social setting in which the disease had occurred. Gradually they had got used to integrating these social factors, giving them the same weight in judging the situation as the patient's symptoms. Clinical diagnosis still played an important part, but it had ceased to be the main object of the examination: was it possible, the question now was, to make the patient's life in society tolerable and worth while?

Organization

To-day the city psychiatrist's department consisted of 45 people, continued Professor Querido, of whom 10 were psychiatrists and 20 social workers. They provided domiciliary supervision for about 3,000 adult mental patients and as many juveniles. The operating cost was about £25,000 a year, without of course any heavy capital expenditure. For administration the city was divided into sectors, each having a psychiatrist and two or more social workers who between them looked after some 400 patients. The psychiatrist took part in the 24-hour roster for emergency calls, and to ensure the close liaison between workers in different sectors that this necessitated there was a staff conference each morning.

When a patient was first seen, full clinical investigation was often necessary. He would be sent to the university clinic, which was visited several times a week by the chief of the service. Here both clinical and social factors were integrated, and a decision was reached on whether the patient should be admitted to hospital or brought under the supervision of the psychiatric service. In the same way, the mental hospitals were visited, though not so often, as it was important to keep before the hospital psychiatrists the fact that their patients were only temporary guests. The first eight months in a mental hospital were critical; if it was not possible to resocialize the patient within that time, the chances of ever being able to do so were slim.

If a patient were placed in the care of the psychiatric service he would be allotted to his appropriate sector psychiatrist, who would decide on the frequency of visiting. It was an iron rule that patients should always be seen at home and without previous warning. Only for special reasons were they invited to the psychiatrist's office. The relationship between the patient and the service was entirely voluntary and no compulsion was used, though obviously lack of co-operation might make admission to hospital imperative. The service was supported by various outside resources, such as sheltered workshops offering temporary employment, foster-homes to tide a family over a crisis or for lonely people, funds for clothes and tools, and an elaborate employment-finding system. These aids, Professor Querido emphasized, were never given as an end in themselves, much less as bribes for good behaviour, but rather as medicines to help recovery.

Prevention

At the start they had been concerned with the management of the adult patient, but as the years went by the service was becoming more and more concerned with prevention. Children at special schools for the feeble-minded had been brought under supervision, and sector psychiatrists were appointed as physicians to these schools. This had led to contacts with teachers in the ordinary schools, who in turn were encouraged to refer children with behaviour problems. They now had a foot in the infant welfare clinics and of course in the children's courts. On the adult side, they had established close liaison with the Bureau of Public Assistance and the City Housing Office, which helped greatly in dealing with problem families, and also in attacks on the so-called "hard core of unemployment."

"I do not want to give the impression that our troubles are over," said Professor Querido in conclusion, "albeit the results obtained up till now seem somewhat startling."

In his Annual Report for 1953 the principal school medical officer of Liverpool, Professor A. B. Semple, reports that at health visitors' cleanliness surveys in schools 19.5% of the children were found, at least once during the year, to be infested. This is a slight reduction on the 1950 figure, but is above the figures for 1951 and 1952. In 59 cases the parents were prosecuted for allowing their children to become verminous after compulsory cleansing, and the Liverpool health visitors all agree that the prosecution of parents where necessary is having a beneficial effect, and the prosecuted parents tend in future to show respect rather than resentment to the health visitors. More could be done to keep children permanently clean if there were powers to deal with the other members of the family.

X-RAY IMAGE INTENSIFIER

[From a Special Correspondent]

A screen-image intensifier has recently been on show in London (see Figure). This is a device for increasing the brightness of the fluorescent screen to such a degree that it is visible in subdued daylight without previous dark adaptation. There is more than one way of doing this, but in this apparatus (made by Marconi Instruments, Ltd.) the method used is, briefly, as follows.

The *x* rays after passing through the patient enter an evacuated glass envelope and fall on a thin metal screen; this screen has the property of emitting electrons when activated by *x* rays, and the electrons thus liberated are then accelerated through the apparatus by means of a high (24 kV) potential difference. By means of several electrostatic fields — "electron lenses" — the electrons, now possessing considerably greater energy, are focused on to a small (one-inch—2.5-cm.) fluorescent screen at the viewing end of the apparatus. This screen resembles the ordinary *x*-ray viewing screen, and emits visible light when subjected to electron bombardment. This image is then magnified up to natural size, reflected out through a glass window, and viewed in a mirror which can be adjusted to any position. The field of view is fairly small (five inches) and the apparatus is necessarily rather large, but it is well counterbalanced and, in the horizontal position, is perfectly easy to use. It is not quite so convenient in the erect position, as the image has to be viewed at an angle and the bulk of the apparatus tends to interfere with palpation of the patient. The detail of the image is remarkably good, and is probably better than can be seen on the ordinary screen.

Special Uses

The tremendous increase in brightness means that the *x*-ray current can be considerably reduced, and ordinary screening of chest and abdomen can be performed using less than 1 mA instead of the usual 3–4 mA. Perhaps the most important feature of this machine is that it is now possible to take excellent cinematograph films (16 mm.) at the standard rate of 24 per second without any danger of radiation overexposure to the patient. By the use of a most ingenious partial mirror which reflects into the camera only light of the wavelength to which the film is most sensitive it is possible to view the screen while the film is being taken and to monitor the field under examination.

The apparatus can be attached to an ordinary *x*-ray couch, and full-sized or spot films may be taken while it is in use. When it is not required it can be very easily detached and pushed out of the way on the ceiling suspension.

It is not suggested that this machine holds any advantage over the conventional apparatus for ordinary routine barium meal and enema sessions, but it is likely to be of particular value in those special investigations which are better carried out in the light and yet in which the operator may need to look at the screen, such as cardiac catheterization, bronchography, retrograde pyelography, and cholangiography. Although the field is not large enough to cover the whole of the adult heart, it should be most valuable for selective cardio-angiography, and is here likely to prove the method of choice. The films taken are of good quality and the barium studies of oesophagus and gastro-intestinal tract are excellent.

Future developments may produce a larger screen, but this will mean, of necessity, a bulkier apparatus. There are limits to the performance of an electron lens, just as there are to ordinary lenses, and a wider field must entail a longer and larger tube; it may well be that about five inches is the optimum screen size. In any case here is an apparatus, available now, which can provide services not obtainable in any other way.

BRITISH PHARMACEUTICAL CODEX

BARRIER SUBSTANCES

Interim Report of the Barrier Substances Subcommittee of the Codex Revision Committee

Barrier substances are widely used in industry to supplement other measures for the prevention of dermatitis from contact with skin irritants. The Barrier Substances Subcommittee has been investigating the possibility of producing suitable standard formulae for a range of protective preparations of this type for inclusion in the *British Pharmaceutical Codex*.

Following the formulation and testing of a number of preparations four have been selected as likely to afford some protection against the commoner forms of hazard and as fulfilling pharmaceutical and cosmetic requirements, but before recommending that the formulae of these preparations should be included in the *Codex* the committee considers that an opportunity should be given for wider experimental use and comment by interested parties, and accordingly is publishing the formulae for this purpose. The committee is aware that the four preparations are similar in character to products which have been in use for a considerable time and that different types of product have been issued recently as barrier substances. The committee is investigating these newer types of product, but considers that until they have been shown to be superior it is desirable that standard preparations of established character should be available. Correspondence concerning the preparations should be addressed to The Secretary, Barrier Substances Subcommittee, 17, Bloomsbury Square, W.C.1.

Provisional Formulae

Dust Barrier

Casein (rennet, finely powdered)	3
Sodium alginate	2
Glycerin	6
Stearic acid	10
Triethanolamine	1.55
Chlorocresol	0.2
Phenol	0.5
Distilled water	to 100

Water Barrier

Hard paraffin	25
Soft paraffin	1.75
Liquid paraffin	3.5
Cetostearyl alcohol	5
Triethanolamine	0.7
Stearic acid	1.8
Chlorocresol	0.2
Distilled water	to 100

Oil and Solvent Barrier

Kaolin (sterilized)	20
Bentonite	3
Hard soap (powdered)	12
Glycerin	6
Stearic acid	2
Sodium chloride	1
Chlorocresol	0.2
Phenol	0.5
Distilled water	to 100

Skin Conditioning Cream

Monostearin, self-emulsifying	10
Glycerin	6
Triethanolamine ricinoleate	1
Wood alcohols	6
Chlorocresol	0.2
Oleyl alcohol	3
Distilled water	to 100

Note.—A suitable non-irritant perfume may be added to any of the formulae if desired.

APPROVED NAMES

In July, 1954, the General Medical Council published a leaflet[1] on "approved names" of drugs, listing all such names issued since 1948, together with names issued earlier for substances which have not become the subject of official monographs. The Council has also authorized the following approved names, selected by the British Pharmacopoeia Commission. The last supplementary list was published in the *Journal* of February 20, 1954 (p. 451).

Approved Name	*Other Names*
Chlormerodrin	3-Chloromercuri-2-methoxypropylurea. "Mercloran"; "neohydrin."
Hydroxyamphetamine	2 - Amino - 1 - *p* - hydroxyphenylpropane. "Paredrine."
Hydroxystilbamidine	4:4′ - Diamidino - 2 - hydroxystilbene.
Levallorphan	(−)-3-Hydroxy-*N*-allylmorphinan.
Melarsoprol	2-*p*-(4:6-Diamino-*s*-triazin-2-ylamino)-phenyl - 4 - hydroxymethyl - 1:3:2 - dithia-arsoline.
Methallenoestril	3 - (6 - Methoxy - 2 - naphthyl) - 2:2 - dimethylpentanoic acid. "Vallestril."
Tricyclamol chloride	(±) - 1 - (3 - *cyclo*Hexyl - 3 - hydroxy - 3 - phenylpropyl) - 1 - methylpyrrolidinium chloride. "Elorine chloride"; "lergine."
Tyrothricin	An antibiotic produced by a strain of *Bacillus brevis*.
Viomycin	An antibiotic produced by certain strains of *Streptomyces puniceus*. "Viocin."

DESIGN OF HOSPITAL BUILDINGS

The Minister of Health, Mr. Iain Macleod, opening a conference on the "Design of Health Buildings" at the Royal Institute of British Architects in London on October 21, said that by the end of the present financial year over £60m. worth of capital works would have been carried out in National Health Service buildings since 1948. Capital expenditure was now running at £11m. a year. But, large as that total seemed, it was nevertheless small in relation to the vast amount of work that needed to be done. They had had to concentrate on comparatively modest works so as to ensure that the money available was distributed as widely and wisely as possible, and that it yielded the most rapid return. Although this was not the ideal state of affairs for the architect, it provided him with a challenge to his ingenuity.

Quite apart from financial limitations, went on the Minister, the advance of medical science was rapidly making the ordinary general hospital less and less a place for lying in bed and more and more a place for concentration within a very limited period of the various skills and techniques that could now be brought to bear. This had meant a fundamental change in the conception of the hospital building itself. Ideally such a change called for an entirely new set of hospitals, but obviously such an objective was unrealistic. The aim must be to adapt existing hospitals to fit the new conception. Running costs were also of great importance.

The Ministry of Health was hoping soon to circulate bulletins on various aspects of Health Service building design and construction. Hitherto central responsibility for the scrutiny of building plans had been exercised almost entirely by *ad hoc* study of each project of any size, and this would continue. But they believed—and the R.I.B.A. were with them in this—that the publication of such bulletins would help architects engaged in hospital planning. In the preparation of the bulletins there would be the fullest consultation with people outside the Ministry—doctors and others, as well as architects—to ensure that the best opinion was canvassed on all points. There was no intention of cramping the architect's initiative by rigid prescription of details, but there were a number of matters, such as space standards, on which architects might well welcome authoritative guidance.

[1] Obtainable gratis from the Secretary, British Pharmacopoeia Commission, 44, Hallam Street, London, W.1.

Nova et Vetera

FIRST MEDICAL V.C.

This week marks the centenary of the first occasion on which the Victoria Cross was won by a medical man, Surgeon James Mouat.[1] Although the V.C. was not instituted until January 29, 1856, several awards were made retrospectively.

At that time there was no separate medical corps, and a medical officer held a commission in the regiment with which he served. During the Crimean War Mouat was surgeon to the 6th Dragoons (now the 5th Royal Inniskilling Dragoon Guards). He was in medical charge of the General Field Hospital of the 3rd Division until the fall of Sebastopol. He was present at the battles of Balaclava, Inkerman, and Tschernaya, and was awarded the Crimean Medal and three clasps. The act for which he was awarded the V.C. followed the charge of the Light Brigade at Balaclava.

On the institution of the V.C. in 1856, the *Association Medical Journal* (February 9, p. 110) expressed the hope that this new order of merit would be given "to the surgeons and assistant-surgeons, as well as the fighting men." In the following year the *Journal* (May 9, 1857, p. 397) protested that despite the remonstrances in the medical press the only medical officer in the Crimea to be awarded a V.C. was Assistant Surgeon Thomas Egerton Hale, for an act of bravery on September 8, 1855. Later in 1857 Assistant Surgeon Henry Thomas Sylvester was similarly decorated, for an act of bravery, also on September 8, 1855.

On June 12, 1858, the *Journal* recorded that "another tardy award of the Victoria Cross has just been made to a medical officer of the army." The official citation, gazetted on June 2, 1858, is as follows:

> "James Mouat, C.B., Surgeon, 6th Dragoons, now Deputy Inspector of Hospitals. Date of Act of Bravery: 26th October, 1854. For having voluntarily proceeded to the assistance of Lieut.-Colonel Morris, C.B., 17th Lancers, who was lying dangerously wounded in an exposed position after the retreat of the Light Cavalry at the battle of Balaklava, and having dressed that officer's wounds, in the presence of and under heavy fire of the enemy. Thus by stopping a severe haemorrhage he assisted in saving that officer's life."

At the time Morris was a captain; he died in India in 1858, having by then been promoted colonel and given a C.B.

Mouat was born in 1815 and received his medical education at University College Hospital. He was M.R.C.S. in 1837 and F.R.C.S. in 1852. He entered the Army as an assistant surgeon in 1848, rose to the rank of Inspector-General in 1864, and retired with the rank of Surgeon-General in 1876. After his service in the Crimea Mouat was in New Zealand during the wars of 1860 and 1863–5; he was repeatedly mentioned in dispatches and received the campaign medal. He was appointed Honorary Surgeon to the Queen in 1888 and K.C.B. in 1894. As a senior medical officer Mouat made his camp inspections in a well-appointed carriage and pair. He died at his home in London on January 4, 1899.

His father, James Mouat, M.D., was an Army officer, and his brother, F. J. Mouat, who had a distinguished career in the Indian Medical Service, was responsible for the introduction of chaulmoogra oil into Western medicine.

[1] *Army med. Serv. Mag.*, 1954, **6**, 107.

Correspondence

Release of Antibiotics

Sir,—With the release of chlortetracycline (aureomycin) and oxytetracycline (terramycin) for general use on November 1, 1954, it is to be hoped that those who have not previously had practical experience of the use of these drugs are aware of the advisability of using them only under bacteriologically controlled conditions. The temptation to use them in uncontrolled fashion is especially great for infective conditions of the skin, but this urge must be firmly resisted. In the first place, it is necessary to find whether the causal organisms are in fact susceptible to one or other of these drugs : in the second place, it is important to know whether there is a mixed flora of organisms some of which may be susceptible and others resistant to the drugs.

When used topically in mixed infections, these broad-spectrum antibiotics may be so successful in ridding the skin of pathogenic staphylococci and streptococci that Gram-negative organisms, particularly *B. proteus*, are left free to multiply unopposed. This particularly applies if aureomycin or terramycin is used in the treatment of otitis externa, infective (flexural) dermatitis, paronychia, or ulcers of the leg, because these are the conditions in which mixed infections with cocci and Gram-negative organisms most often occur. The resultant ecological infective dermatitis is difficult to control because of the resistance of *B. proteus* to most antibiotics. It is best to adopt the policy of trying to reduce the excessive growth of *B. proteus* on the skin by cleansing with a bactericidal quaternary ammonium compound such as 0.5% "bradosol" or 1.0% cetrimide. This treatment is, in fact, often preferable in the first instance when a culture reveals a mixed infection of cocci with *B. proteus*. When penicillin was introduced, there followed an outcrop of penicillin sensitization reactions. With these broad-spectrum antibiotics one anticipates with some dread an increase of ecologically induced infective dermatitis due especially to *B. proteus*.—I am, etc.,

London, W.1 Brian Russell.

The M'Naghten Rules

Sir,—According to the theory of determinism, those who accept or reject the theory are equally without choice in the matter. There would appear to be no means of determining the validity of the theory, as investigators would be without choice as to their verdict. In my opinion, determinism is best considered with *Alice Through the Looking-Glass*, and not made a basis for legal or other systems involving human conduct.—I am, etc.,

Wolverhampton. J. D. Baston.

Sir,—In my schooldays I produced the following argument on free will. Suppose there is an omniscient being who knows the future as well as the past, who knows that you are going to turn right at a cross-road. This is all very well, unless he lets you share his knowledge, when I maintain that you are capable of turning left : which is absurd. The trouble is that this rather Socratic argument, in addition to proving free will, also disproves the possibility of a being who is both omniscient and omnipotent. As I brought it out in a confirmation class, the result was that I began my medical studies rather earlier than usual.—I am, etc.,

London, W.1. Denis Browne.

Sir,—I have only just read, but read with great interest, Dr. Eliot Slater's article (*Journal*, September 25, p. 713) "The M'Naghten Rules and Modern Concepts of Responsibility." True that in the light of modern psychiatric knowledge the M'Naghten rules may well be an inadequate basis of assessment in criminal cases, but when he states "no theory of mental medicine could develop without the working hypothesis of determinism," and that "the 'free will,' on which both law and religion are based, proves a heuristically sterile idea," he would appear to suggest that common law and medical practice should nail their flags to a theory which may or may not prove true (or more likely never be proved either way), rather than take their stand on common sense. Further, when he goes on to state "if we attempt to inject it [free will] into our analysis of causation it only introduces an element of the unknowable," he assumes that man possesses the necessary cerebral machinery to understand the real nature of things for which surely there is little evidence. Rather, is not modern physics against him ? Does it not teach us that there are certain things which the mind of man cannot directly apprehend ?

Now I do not know if my will is free or not, but I do know that I and everyone else (including Dr. Slater) live as if it were. "All theory is against it [free will]," said Dr. Johnson (Dr. Slater is advocating nothing new), "all experience for it." And after two hundred years that is still the position. Surely in the present state of human knowledge we would be wise to continue to trust human experience rather than run off after psychiatric theory. Under existing circumstances common law and medical practice will be better advised to stick to the wisdom of Dr. Samuel Johnson rather than allow themselves to be seduced by the high intellect of Dr. Eliot Slater.—I am, etc.,

Gt. Abington, Cambs. A. E. Clark-Kennedy.

Flourpaper Tuberculin Jelly Test

Sir,—Drs. M. Caplin, June Harrington, C. P. Silver, and S. Grzybowski (*Journal*, October 16, p. 895) have performed a most important and exhaustive investigation into the real significance and value of the tuberculin jelly test. I would like to draw special attention to the following extract of their report: "Despite careful use of the flourpaper the majority (all but 28) of the 173 Mantoux-negative children showed some reaction at some time. . . . In these Mantoux-negative children a reaction elicited by the control jelly was much less often seen and was always less severe than the reaction due to tuberculin jelly, though one would have expected them to be the same. We are unable to account for this surprising finding, as the only apparent difference between tuberculin and control jelly is that of tuberculin content."

I have drawn attention to this "false positive" in these columns before (*Journal*, May 1, p. 1039, and June 26, p. 1496). In the report under discussion 10% of Mantoux-negative reactors are classed as jelly positive under a standard "B." In a group of children taken at random from general practice in 1952–3 12% false positives were found. These are now being tested a year later and many are now negative reactors to jelly. Unlike the present authors, and others who have tried to explain this phenomenon, I do not accept a trivial or mechanical explanation for the awkward fact. For some reason at present not known the human epidermis is allergic to tuberculin while the cutis is not, for the control jelly causes very little reaction in these cases.

L. Negre and J. Bretey[1] think that a mild avirulent tuberculous infection is possible in guinea-pigs and have described transient hypersensitivity to tuberculin. These avirulent infections were so mild as to become abortive in the host, to fail on transfer to a new host, and to become extremely difficult to culture. The writer feels that the so-called "false positive" may later be accepted as a "transient positive" not associated with classical signs of a primary focus, but clearly arising as a result of a pre-tuberculous state which has not yet been defined because we are blinded by the traditional picture of early tuberculosis. Let us admit with the authors of this report that we are unable to account for this surprising finding. Let us not assert with dogmatism that it is false, for thereby we must obscure the truth, which is at present ahead of our knowledge on this subject.—I am, etc.,

Romford, Essex. P. D. Mulkern.

Reference

[1] *Amer. Rev. Tuberc.*, 1953, **68**, 467.

Sexing the Unborn Foetus

SIR,—We were interested to read Dr. G. I. M. Swyer's comments on sexing the unborn foetus (*Journal*, October 16, p. 930). Some months ago we performed a small number of the Rapp–Richardson tests, with the following results: out of a total of 51 tests, 26 results were correct and 25 incorrect. Of the positive results, indicating a male foetus, 6 were correct and 9 incorrect. Of the negative results, indicating a female foetus, 20 were correct and 16 incorrect. The total number of tests performed was small, but indicated its inaccuracy. Whilst some of the mothers took the whole experiment in as light-hearted a manner as we ourselves tried to adopt, many were disappointed when told the result and their fears were either confirmed or denied on the baby's arrival. Others, delighted to be told that a boy (or girl) was expected, were upset when the opposite sex arrived.

A recent newspaper article suggested that a foreknowledge of the sex of the child was important "because mothers want to know whether to buy pink or blue." We considered that the peace of mind of the mother was more important than the colour of a piece of wool, and we discontinued the tests as soon as we saw the trend of the results.—We are, etc.,

H. FRANK.
GERALD W. KORN.

Enfield, Middlesex.

Industrial Dermatitis

SIR,—Dr. F. Ray Bettley, in his very practical article on this subject (*Journal*, October 16, p. 905), states that, in order to get a detailed description of the patient's work and of the substances with which he comes in contact, "information should be obtained from the factory manager or chemist if possible." Commenting as medical officer to a group of large engineering factories, I agree that, for doubtful cases of dermatitis coming from small factories where there is no medical supervision, that is possibly the only way of getting the desired information in order to establish a correct diagnosis. In such cases coming from larger factories and establishments where there is medical supervision, I would suggest that Dr. Bettley should seek for information from the industrial medical officer, who not only sees these cases in their earliest stages, even before the family doctor, but who is also fully conversant with all the details of the patient's industrial environment. As I pointed out at the last Annual Meeting of the B.M.A. before the Section of Dermatology, a closer contact and liaison on these lines between dermatologists and industrial medical officers would be to their mutual advantage in helping to solve their interrelated problems concerning industrial dermatitis.

Regarding the use of barrier creams, some members of the legal profession, in dealing with claims for compensation, seem to assume that for every physical and chemical agent which can produce dermatitis by contact with the skin there is a specific barrier cream which ought to be used as a preventive measure. Such, of course, is not the case. There is an increasingly large number of substances used in industry for which there is at present no known barrier cream which is effective. Thus in the same issue of the *Journal* (p. 938) "Any Questions?" item "Oil at Work," your contributor states that "barrier creams are readily penetrated by oils." This conforms with my experience that barrier creams, in the present state of knowledge concerning them, can play no important part in the prevention of oil dermatitis.

I believe that a constructive and rational approach to the use of barrier creams in industry would be as follows. If an employer has established by various measures, and maintains, a safe system of working, and if his employees at risk co-operate by using regularly the washing facilities provided for them, by changing their personal protective clothing (overalls, etc.) at least once per week, by wearing any items of supplementary protective clothing such as gloves, armlets, aprons, leggings, etc., considered necessary to protect them, and if cases of occupational dermatitis still occur, then, and only then, should the use of barrier creams be considered, with the following conditions applying: (1) the barrier cream which it is intended to use must have a specific neutralizing action on the particular skin irritant involved. (2) The manufacturers should make known the constituents of the barrier cream, if necessary under confidential conditions. (3) The barrier cream must be harmless to the skin. I know of employees who have used non-specific barrier creams as a substitute for soap and water with disastrous results to their skins. (4) The barrier cream should be easily applied to, and equally easily removed from, the skin.

Finally, may I point out that the "certifying surgeon," so designated in Dr. Bettley's article, is now known as "the appointed factory doctor"?—I am, etc.,

E. COLLIER.

Glasgow, S.W.2.

SIR,—I read the article by Dr. F. Ray Bettley (*Journal*, October 16, p. 905) with much interest, but there are some points which arouse comment. Dr. Bettley writes "he [the G.P.] is usually required to issue a certificate at once and decide definitely whether the eczema is industrial or not." This is not so. It is not necessary for the G.P. to decide at once. In fact, if the patient is unfit for work, all the doctor has to do is to issue a certificate for dermatitis and tell the patient he is not certain of the cause. The local insurance office refers all cases of dermatitis to the district examining medical practitioner. The title "certifying surgeon" was changed to "appointed factory doctor" by the Factories Act, 1948. The appointed factory doctor is generally a G.P. and is appointed by the Ministry of Labour. He usually holds the post of examining medical practitioner for the Ministry of National Insurance, and in this capacity decides whether the cause is occupational or not. If he decides that it is not, the patient may appeal and is referred to a dermatologist for another decision. If the examining medical practitioner decides that the complaint is occupational dermatitis, scheduled disease 24(b), industrial benefit is paid, but if still off work after 13 weeks the patient is referred automatically by the Ministry of National Insurance for a medical board.

It must be exceptional for an action in common law for dermatitis to be brought within six months of the event, which allows for some consideration, and although the decision of a medical board or appeal board may not be allowed as evidence in favour of industrial origin their evidence against would probably carry some weight.

There has been considerable dissatisfaction among examining medical practitioners that the opinion of the dermatologist, particularly if it reverses their own, is not automatically passed to them for information. The dissatisfaction is understandable, but there is this additional point that they see every case which may be occupational in origin whereas the dermatologist sees only a selection of cases, usually of many weeks' duration. In many cases, as Dr. Bettley admits, it is impossible to make a certain diagnosis. The patient is given the benefit of the doubt. In any case after 13 weeks the complaint may have altered beyond recognition, occasionally becoming dermatitis medicamentosa or frankly psychosomatic. The examining medical practitioner has usually a much more intimate knowledge of industry and of industrial processes than the dermatologist or ordinary G.P. It would appear that there is scope for a closer association of examining medical practitioners and hospital departments of dermatology.—I am, etc.,

M. E. M. HERFORD.

Farnham Royal.

Angular Stomatitis and Artificial Dentures

SIR,—It is indeed gratifying to feel that one's efforts have been considered worthy of further comment. There is no doubt that helpful criticism does much to advance scientific knowledge, and Dr. R. Earnshaw and Mr. D. C. Smith have certainly given me food for thought in their letter (*Journal*, July 24, p. 242). It is obvious that their dental knowledge is much greater than mine, and I would not venture to cross swords with them when they state that it is not standard practice to close a patient's normal bite. Perhaps I was working in an area where considerable bad dentistry was perpetrated, as this personal observation was not denied by my technical advisers. Moreover, the fact remains that

our efforts to correct this non-existent state by opening the bite was not without a certain measure of success.

Further, I would not deny their statements regarding the retention of monomer in dental plates; but thought I had put up a reasonable argument against its being a factor in production of sensitivity. However, I am not prepared to admit that delay in showing sensitivity reactions is a valid argument against its existence, as it is a well-known dermatological fact that a person may suddenly develop sensitivity to a substance with which he has been in contact for many years, the exact mechanism of this not yet being fully understood.

Finally, I must confess that I accepted positive patch tests as definite evidence of sensitivity without considering the interesting possibility they mention, and think that their suggestion is well worth following up; but did do a number of tests in normal subjects with scrapings which had given positive reactions previously, without producing any such positives in anyone other than the person wearing the dentures. However, their theory might well account for my case No. 7, although I assumed here that the failure to reproduce the original positive was due to loss of sensitivity, again a comparatively well-known phenomenon.—I am, etc.,

Timaru, New Zealand. J. G. HARKNESS.

Surgical Induction of Labour

SIR,—As a general practitioner with 16 years' experience of domiciliary surgical induction of labour, I was interested in the papers by Drs. R. A. Tennent and M. D. Black (*Journal*, October 9, p. 833) and Hector R. MacLennan (p. 837). The conditions for which I induce are similar to those described in the papers—i.e., prolongation of pregnancy, previous big babies, toxaemia, potential disproportion, and one case of a previous caesarean section. I am of opinion mothers should not be told a definite date for labour. When it does not happen on the appointed day they become anxious. I usually give them a fortnight—a week before and after term—during which to expect the baby.

My experience of the "latent period" is rather different from that of Drs. Tennent and Black. Most of my cases came into labour within 10 hours of induction. The longest was a moderately contracted pelvis which took 19 hours. I think the latent period is bound up with the technique of induction. Apparently the authors merely puncture the membranes and allow the liquor amnii to drain away slowly. I always puncture the foremembranes with a catheter stylet. I do not used the D. Smythe catheter, which does not imitate natural rupture and only drains the liquor slowly. It is most important to get a quantity of fluid away at once, and this I do by pushing the head up and down with a finger in the cervix. At first there is little flow, but very soon the liquor comes down in gushes along the palm of the hand. I do not measure this, but I know from experience when to stop. I have found that the more liquor amnii I can get away the sooner labour starts. Also I allow all cases except those with relaxed muscles and mobile babies up and about. At first I was afraid of cord prolapse, but so far this has never occurred.

I agree that many women who have reached term, unless they are known to have had previous small babies, are better induced within a week or so. I agree also that women who have had previous big babies should be induced before term. Big babies cause subsequent disability—that is, pelvic discomfort, various degrees of prolapse or incontinence. Such women have to stop playing games and may soon have to lie down every afternoon. I look upon every primigravida and some multiparae as cases of potential disproportion. I only use the simplest methods of observation—that is, three external measurements, abdominal projection, on which I chiefly rely, and a bimanual examination at the 37th week. In the interests of the baby I will not do induction earlier than this, though with the development of premature baby units it may soon be possible, even if seldom necessary. I am not converted to the need for submitting women to a general anaesthetic in order to explore the pelvic architecture, and I am still dubious of the advantages of *x*-ray pelvimetry.

In no case of my series was caesarean section necessary after induction of labour. Forceps was used in two or three toxaemic cases. Though the series was small in comparison with the 1,585 cases of Drs. Tennent and Black, there was no significant morbidity even in pre-penicillin days. The old fear of sepsis complicating caesarean section after induction should have less force to-day. I have heard it said that caesarean section becomes a boring and easy operation. If there is a reaction against it we may soon see trial induction, trial labour, and even trial forceps the order of the day with section reserved for failures.—I am, etc.,

Smethwick. E. CONDON.

SIR,—The paper on this subject by Drs. R. A. Tennent and M. D. Black (*Journal*, October 9, p. 833) is full of interest and shows the result of a great deal of industry, but the title might have been "Is Meddlesome Midwifery a Good Thing?" The percentage number of surgical inductions is 18.3. This year in the Maternity Hospitals in the Free State the percentages were, respectively, for Rotunda, National Maternity, and Coombe, 3.5, 3.2, and 1.7.

There are many points one could criticize. I *know* from my experience that the teaching, "No regard has been paid to the condition of the cervix," may be disastrous for the women of the world, for general practitioners who read this article may well follow this technique with serious, if not disastrous, results. The paper would certainly have been more valuable if, for instance, the condition of the cervix had been given in those 166 cases which failed to fall into labour in 72 hours: 21 multiparae required caesarean section after induction; these figures require explanation. The introduction of chemotherapeutic and antibiotic substances should not be used as an excuse for unnecessary interference.—I am, etc.,

Dublin. BETHEL SOLOMONS.

Coagulation Defect in Accidental Haemorrhage

SIR,—I have read with interest Dr. H. C. Moore's report (*Journal*, July 31, p. 277) of coagulation defect found in accidental haemorrhage. The following is a report of a similar case.

The patient, a 6-para, was admitted on September 12, 1954. Her first delivery had been by forceps, but the others were normal. She gave a history of having had pains for three days, bleeding by mouth the previous night, and some bleeding per vaginam. As she had pyorrhoea, and the gums were inclined to bleed, it was thought that this was what she meant. On examination, she looked anaemic, her blood pressure was 104/80, the urine was loaded with albumin, Hb 62% (Sahli), and no foetal heart could be heard. On vaginal examination, the os was two fingers dilated, the membranes were bulging, and were ruptured during the examination. She was having slight pains. The vaginal bleeding increased, and the question of caesarean section arose. However, it was noted that the vaginal blood did not clot. The clotting time was 5½ minutes, and the bleeding time was more than 15 minutes. It was therefore decided not to operate. The patient then had a fairly large haematemesis; her blood pressure had fallen to 90/50, and her condition gave rise to anxiety. An intravenous saline drip was started pending the arrival of blood. In addition she was given vitamin K ("synkavit"), vitamin C, 1,000 mg., and calcium gluconate, also intravenously, and "coagulen-ciba" intramuscularly, in the hope that there would be some beneficial effect. (Incidentally, the blood bank officer telephoned to ask why we had sent citrated blood.) Niggling pains continued, and the patient was sedated with pethidine, 100 mg. The next day a stillborn baby boy weighing 6 lb. 3 oz. (2.8 kg.) was delivered normally. There was a large retroplacental clot.

After delivery the patient's condition improved, although there was profound anaemia (Hb 38%). Four days later the bleeding time was 6 minutes 45 seconds, and clotting time 4 minutes 40 seconds. Albumin disappeared from the urine on the ninth day. The patient is still undergoing treatment for anaemia, but is otherwise well.

I have to thank Dr. Samuel for access to the case notes, Dr. Coyaji for advice, and Dr. A. Rankine for permission to publish this case.—I am, etc.,

Poona City. M. A. HARVIE.

A Penalty of Partial Gastrectomy

Sir,—The results of partial gastrectomy in selected cases of peptic ulcer appear to be eminently satisfactory. Patients are able to cope with their various occupations in civilian life better after their operation than before it. It therefore came as rather a surprise the other day to hear from a patient that he is at present unemployed because of his stomach operation.

This patient, Mr. R., a commercial traveller, had a gastrojejunostomy in 1936 for a duodenal ulcer. In 1939 duodenal symptoms recurred, and thereafter he suffered periodically with occasional small episodes of haematemesis. Eventually a more prolonged attack ensued, his firm paid him off, and he came into hospital in May this year. A retrocolic partial gastrectomy of the Polya type was performed, removing the duodenal ulcer and a stomal ulcer. He made an excellent recovery, and after a holiday started to look for work again in September, feeling better than he had done for many years. When he reported on October 4 he was feeling very well, was putting on weight, but he was still out of work. He had had 22 interviews for employment as a commercial traveller, but he had been turned down at every one, not because of lack of references, but because he had been out of employment since May, and "after a stomach operation he was not considered fit to undertake the duties of a commercial traveller." He had pointed out that he had been working as a traveller all the years after his first operation (the gastrojejunostomy) and was actually better at present following a second operation, which was considered to be a cure. But this apparently cut no ice, and at one interview he was examined by a doctor who looked at the abdominal scars and remarked that he would turn down Mr. R. "for his own sake," as he was not fit to stand up to the life of a traveller in such a state.

It seems that some lay employers regard a man who has had a modern operation for peptic ulcer as crippled, not cured. The down-grading of a man with a proved peptic ulcer is understandable in the Services, but where is the line to be drawn in civilian life? One can understand employers hesitating to take on a man who has been off sick repeatedly in the past; and undoubtedly a commercial traveller's life, with its irregular meals, is not a suitable one for a peptic ulcer patient. But if the patient has had a partial gastrectomy, he should be in a much better condition to stand up to such conditions. Mr. R. certainly should be, as he was suffering from a stomal ulcer as well as a duodenal one; and he is now, in fact, in excellent health. It is rather surprising that a doctor, knowing the technical details, and conversant with modern literature, should have concurred with the adverse opinions of the laymen, and advised against employing Mr. R. for his own sake.

The experience of this patient raises some disturbing thoughts, and shows that an operation which is performed so frequently and with so much benefit appears to carry the serious penalty of loss of employment in certain quarters, a factor which must be duly considered when recommending gastrectomy, particularly to a commercial traveller. The experience and opinion of your readers in relation to this problem would be interesting.—I am, etc.,

Edinburgh. James A. Ross.

Rheumatic Diseases Hostel

Sir,—Some months ago Bracken Hill House, Northwood, Middlesex, was opened by Miss Hornsby-Smith, M.P., as a hostel for early sufferers from rheumatic diseases. It is intended for those who live too far from a rheumatic centre for daily treatment as somewhere for them to stay and be looked after while they receive appropriate early diagnosis, guidance, and treatment at near-by Mount Vernon Hospital. It is well known that cases of active rheumatic disease do better if they can rest and relax completely during their treatment, away from the worries and responsibilities of their daily round, whether it be in business, industry, or in their own household chores.

This venture was started by the British Rheumatic Association and sponsored by Lord Nuffield. All who saw it or heard of it applauded the concept and spoke of the tremendous need there was for it. It was cited as the perfect British compromise of private charitable enterprise and the State service. The benefits to those patients who have already visited the hostel have been most encouraging, but the response in numbers has been disappointingly small. We can only assume that our efforts to publicize the experiment in the press and elsewhere have not reached a wide enough public. In particular, family and industrial doctors, who are most likely to send us patients, have not heard of the scheme nor appreciated the help we can give their rheumatic patients. The charges are reasonable: seven guineas a week for a single room; 5 guineas a week for a double room; and £4 15s. a week for a room with three or more beds. There are no other charges whatsoever, as all treatment at Mount Vernon Hospital is free under the N.H.S.

This letter is written in the hope that anyone interested will write for details and application forms either from the Matron, Bracken Hill House, The Woods, Northwood, Middlesex, or direct from the British Rheumatic Association, 11, Beaumont Street, London, W.1.—We are, etc.,

Martin Stratford.
Northwood, Middx. Dudley M. Baker.

Appendicectomy in Chronic Appendicitis

Sir,—Dr. Ian G. Wickes (*Journal*, October 9, p. 869) says that the paper by Mr. I. McLennan and Mr. J. K. Watt (*Journal*, September 25, p. 736) appears to be a product of confused reasoning. Dr. Wickes's letter serves as an excellent demonstration of one of the mechanisms of confused reasoning. Dr. Wickes points out that appendicectomy has cured the abdominal pain in 80% of these cases, but that this does not establish the diagnosis of chronic appendicitis. He is affected by the frustration of the unknown aetiology, and allows the effect to break out in the statement that laparotomy (through a grid-iron incision) is often followed by recovery—though McLennan and Watt expressly state that a grid-iron incision is inadequate for this purpose. Dr. Wickes then escapes, as is so usual among the frustrated, into a comfortable woolly-thinking cloud of purely functional diagnosis. It is certain that this 80% of recoveries were not functional pains. All functional symptoms have their deeper-seated causes. The removal of the symptom without touching the root cause does not lead to recovery, but either to relapse or the outbreak of an alternative symptom.

McLennan and Watt have shown that appendicectomy can bring about recovery in certain cases of abdominal pain of unknown aetiology which are commonly and perhaps inaccurately diagnosed as chronic appendicitis. To stir the emotions, may I hazard the suggestion of varicose veins? In the appendix? Whoever heard of them? Whoever looked for them? Patient thin, undernourished, anxious, with visceroptosis, and consequent occasional venous congestion. Quite impossible to demonstrate at operation and necropsy. That which we cannot prove does not exist and is therefore functional, and so reprehensible because frustrating—which is where we came in.—I am, etc.,

Crowthorne, Berks. H. D. Forbes Fraser.

The Weight of the Thymus

Sir,—Some former work of my own on the above subject has been recalled to me by the very interesting paper of Mr. Geoffrey Keynes on "The Physiology of the Thymus Gland," the Thomas Young Memorial Lecture (*Journal*, September 18, p. 659). In 1920, while I was doing some private research on infant crania (stillborn and non-viable) at the Liverpool City Laboratory by courtesy of Dr. J. M. Beattie, he asked me if, as a matter of interest, I would weigh the thymus. I readily assented, and did so in many of the subjects. The results of this particular work were duly

recorded by me at the time, but never used. I have Dr. Beattie's sanction in now bringing them forward.

The thymus was weighed and briefly inspected in 113 cases. Thirty-nine were of body weight 1¼–5¼ lb. (0.7–2.6 kg.), and 74 around term—6–11 lb. (2.7–5 kg.), average 7¼ lb. (3.2 kg.). In these 74 (42 males, 32 females) the average weight of the thymus was 10.5 g. Friedleben[1] gave 14.3 g. for the same period of life, the lowest figure I have found cited in the literature being that of Sappey,[2] 3 g. The great diversity of findings for the thymus may very probably be explained by two curious features, the weight spread and the weight range. With regard to the first, there was in the present series little sign of the clustering about the arithmetical mean which biological material so commonly shows. Reading the following figures as "numbers of glands of not more than 3 g., over 3 but not more than 4 g.," and so on to the end, they were: 2, 2, 3, 7, 5, 4, 8, 2, 6, 7, 6, 5, 7, 3, 2, 3, 1, 1. The second feature, the weight range, is sufficiently declared by these figures: the actual extremes here were 3–21.5. A mass range of this order for a maturely functioning organ under like conditions is, so far as I know, quite without parallel, and invites comparison with the variability of some vestigial structures. Among the 113, light and heavy glands were met with in either sex, and the sex difference observed by Bratton[3] was not decided enough to be obvious in a series of this length.

Judging from the evidence of the remaining 39 in various foetal stages, thymus growth is positively correlated with general body growth till full term. In these immature subjects, also in those at term, I quite frequently found, as Astley Cooper is stated to have found in the calf and human foetus, "milky fluid" in the glands. The fluidity appeared limited to the medulla, the cell contents, in the few filmed, being almost entirely mononuclear. As mine cannot be an isolated finding, one must suppose that this excess water content will have influenced other post-mortem estimates of the average weight of the thymus at birth. Of the above 74, 69 were examined for fluidity, of which 17 (24.6%) showed it in more or less marked degree, their average weight being 13.4 g., as compared with 9.4 g. for the 52 without fluidity, the weight range of the latter being 3–21 g.

Mr. Keynes, commenting on Astley Cooper's findings, says "it is notorious that the thymus disintegrates very quickly after death," and testifies from his surgical experience that "the freshly removed human thymus, even in very young children, is almost entirely solid." From these statements one is led to conclude that he regards the occurrence of fluidity as a post-mortem change, and so I myself assumed at first. However, apart from the fresh condition of most of this material (1–3 days old), in one subject—7¼ lb. (3.3 kg.)—showing, by exception, commencing putrefactive changes, the thymus (11 g.) showed no fluidity, nor was it present in any of 6 macerated subjects up to term. With the object of testing the point further, I immersed two glands (9.8 and 12.5 g.) which felt solid in physiological saline for 3–4 days, at the end of which time no fluidity was found. I was therefore left in some doubt. If this be a post-mortem change, it is at any rate remarkably inconstant.—I am, etc.,

Preston. EDMUND HUGHES.

REFERENCES

[1] Cited by J. K. Friedjung in *The Diseases of Children*, 1908, edited by Pfaundler and Schlossmann, volume 3, p. 426. Lippincott, Philadelphia and London.

[2] *Human Anatomy*, 1907, edited by Piersol, p. 1797. Lippincott, Philadelphia and London.

[3] *J. Path. Bact.*, 1925, **28**, 609.

The Staining of Serum Proteins

SIR,—The facts to be described began with the observation by Mr. G. W. A. Salmond, technician at Stracathro Hospital, that a drop of serum diluted with four parts of distilled water, dried on a glass slide, and then fixed shows differential staining with the cytoplasmic part of a Masson's trichromic method.[1] The centre takes the blue dye (C.I.707), and a thin peripheral ring the red dye (C.I.89). This led him to try abnormal sera, and these showed that a serum with low albumin gave a paler staining with the blue, whereas high serum globulin gave a broader and more strongly stained red ring. He then demonstrated that a dried drop of diluted gamma globulin was coloured intensely red overall, and that a mixture of bovine albumin and gamma globulin gave again a pale blue centre with a red ring.

With the assistance of Mr. Fraser, technician at the Royal Infirmary, Dundee, these findings have been confirmed, and enlarged by the application of a wide variety of other staining methods. The simplest of the demonstrative methods is the use of the combined cytoplasmic solution of Gomori's trichromic method,[1] which gives excellently clear results on these drops. Electrophoretic paper strips (kindly supplied by Dr. J. H. Prain) have also been studied. These are fixed, as are the dried drops, by formol sublimate[1]; after staining with Gomori's solution for one hour, followed by washing in 1% acetic, dehydration, xylol clearing, and impregnation with B.P.S.,[1] we have obtained green staining of the albumin fraction and red staining of the globulin fractions. It is not yet clear that there is any immediate practical application of Mr. Salmond's most interesting observation, but it is obviously a fact worthy of note, and one likely to interest those who work with proteins or with dyes.—I am, etc.,

Dundee. A. C. LENDRUM.

REFERENCE

[1] *Recent Advances in Clinical Pathology*, 1951, edited by S. C. Dyke. 2nd ed. London.

Accidental Carbon Monoxide Poisoning

SIR,—Dr. Keith Simpson's experience of the causes of accidental deaths is such that anything he writes commands attention (*Journal*, October 2, p. 774). The gas industry regards as most valuable, and can confirm, the analyses which he gives in his article on "The Danger of Accidental Carbon Monoxide Poisoning"; and it welcomes his reminder to consumers about the importance of seeing that their appliances and installations are properly maintained, for it devotes much of its publicity to that subject. It is to be regretted, however, that apparently he did not inform himself of what the gas industry has done and is doing in the interests of safety. Had he done so, he could not have said that "the apparent unconcern with which the gas authorities take this alarming toll of life is astonishing." The statement is as unfair as it is inaccurate.

For many years the industry has given earnest attention to safety, and its efforts have been intensified since the area boards took over control. Its view has been that safety begins with the design of appliances and sound installation. Before being placed on the industry's approved list all new types of appliances and fittings are tested in the industry's laboratories; and the boards buy only appliances on this list. Safety is the first requirement in any test. A special committee appointed last May is giving priority to the study of possible modifications in design and of devices still further to promote the safety of appliances. Particular account is being taken of the large proportion which accidents in the higher age groups bear to the total number. The use of simple types of safety taps on supply pipes and appliances has been extended since the war. All taps on cookers now approved are of the safety type. During the last four years old cookers have been replaced by modern appliances at the rate of some 350,000 a year. Day and night emergency services are maintained, and immediate attention is paid to any report of an escape. Notices appear on meter cards and gas bills and are posted in showrooms telling consumers what to do if they have the slightest suspicion of a leak of gas.

Dr. Simpson suggests that gas radiators, stoves, refrigerators, and geysers shall all have vents. If by geysers, bath water heaters or multi-point heaters are meant, adequate flueing is standard practice; but flueing is not required for instantaneous sink water heaters or storage heaters or for the other appliances he mentions any more than for a gas-lighting burner. The boards would never fit a flue to an appliance giving bad combustion: the appliance would be put right or it would be removed. With regard to the "common meter," no board would install, or knowingly allow to remain installed, a prepayment meter to serve more than one occupancy. Pamphlets of the Royal Society for the Prevention

of Accidents and of the Interdepartmental Fire Prevention Committee include advice that, before a coin is inserted after a supply has run out, care should be taken to see that all taps are turned off. Out of a total of some 12,000,000 domestic consumers, nearly 8,000,000 have prepayment meters. The number of deaths classified as "prepayment meters giving a restarted supply" has averaged 10 a year for the past few years, or approximately 2% of the total number of fatalities; and this includes all prepayment meters, not only "common meters," a very small proportion of the whole.

Dr. Simpson refers to fractured mains outside premises. Fatalities due to escapes from mains and services were 20, 14, 24, and 5 in 1950, 1951, 1952, and 1953 respectively. He implies that the existing cast-iron mains are out of date by comparison with "drawn" pipes. Underground pipes are required to be strong and also to resist corrosion, and the pipes used by the industry meet both these requirements. Where mains and services are known to be in bad condition they are renewed, but the number of deaths—averaging 1.3 per million consumers for the four years quoted—shows that the risk from escapes of this nature is very small. The report of the Home Office Standing Interdepartmental Committee on Accidents in the Home places the commonest kinds of fatal accident in the following order of importance: falls 58%, burns and scalds 13%, suffocation 12%, and, last, coal-gas poisoning 8%. Whatever the relation of gas accidents to the total—and the figures for gas accidents include open verdicts—the industry is very much concerned to see that the use of gas shall be as safe as possible and proof against human carelessness as well as physical disability.—I am, etc.,

London, S.W.1. F. G. Brewer,
Secretary, the Gas Council.

Normal Cerebrospinal Fluid Sugar in Tuberculous Meningitis

Sir,—My letter (*Journal*, September 11, p. 646) has, I am glad to see, raised considerable interest in this finding. As reduction in mortality depends upon early diagnosis, I hope that pathologists will be stimulated to make as thorough an examination of the Z.N. film in these cases as they would when the sugar concentration is reduced. Dr. Esther H. Welbourn (*Journal*, October 16, p. 930) asks whether the case to which I referred had a convulsion previous to lumbar puncture. The answer is that she has had no convulsions at any time during her illness. Her statement that "polymorphs predominate in the C.S.F. towards the later stages of the disease" is, in my view, incorrect. In my three years' experience of examining specimens from a busy tuberculous meningitis treatment centre I have never seen a single case exhibiting this phenomenon and perusal of textbooks leads me to believe that it does not occur. Furthermore, in the case which I reported the sugar concentration did fall on two occasions to 38 mg. and 45 mg. per 100 ml.; the leucocyte counts being (per cubic mm.) 700 (70% lymphocytes) and 192 (90% lymphocytes) respectively.—I am, etc.,

N. Ferriby, Yorks. J. G. Alexander.

International Anatomical Nomenclature

Sir,—I am glad to read in Professor T. B. Johnston's letter in your issue of July 24 (p. 243) of the "sweet reasonableness" which characterized the meetings of the International Anatomical Nomenclature Committee, and I only hope that this spirit of Locarno extends to the teachers of clinical medicine and surgery, who by no means took kindly to the forcible infliction of the cumbrous and abominable Basle nomenclature on their unhappy students in about the year 1910. I was one of the latter, so I "speak that I know." If further changes are contemplated, the anatomists have until July, 1955, to get in touch with the clinicians, whose point of view, quite reasonably, is that it is more important for a student to understand his teacher—and *vice versa*—than for a professor in Berlin to use the same technical jargon as his brother in Japan.—I am, etc.,

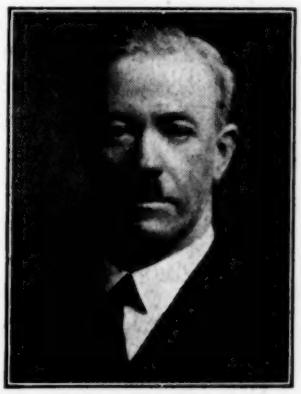
Tanganyika. H. Williamson.

Obituary

DONALD McINTYRE, M.B.E., M.D., F.R.C.S.Ed., F.R.F.P.S., F.R.C.O.G.

The death occurred in a Glasgow nursing-home on October 20 of Dr. Donald McIntyre, one of the leading gynaecologists in the west of Scotland. He was 63 years of age.

Donald McIntyre was born at Greenock on July 29, 1891, and was a student at Glasgow University, where he graduated M.B., Ch.B., with commendation, in 1914. He entered the R.A.M.C. and served for four years in the first world war in the Dardanelles campaign and in East Africa, being appointed M.B.E. in 1918 and mentioned in dispatches. On demobilization he was granted the rank of honorary major.



Returning to civilian life, McIntyre devoted himself to the study of obstetrics and gynaecology, taking the diploma of L.M. at Dublin in 1919 and the F.R.C.S.Ed. in the following year. He joined the staff of the Royal Samaritan Hospital for Women, Glasgow, in 1920 as pathologist, a post which he held for seven years. In 1921 he became a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow, and in 1926 he proceeded to the M.D., with honours, being awarded the Bellahouston Gold Medal for his thesis. In the following year he gained the Struthers Gold Medal and Prize from Glasgow University and was elected a Fellow of the Royal Society of Edinburgh. In 1923 he was appointed assistant surgeon to the Royal Samaritan Hospital for Women, and four years later he became surgeon in charge of wards. McIntyre had been senior consulting gynaecologist to the Royal Samaritan Hospital for Women since 1936, and a member of the board of management of the Glasgow Maternity and Women's Hospitals Group since the inception of the National Health Service. Other appointments he held were Royal Samaritan Lecturer in Gynaecology, Glasgow University; consulting obstetric surgeon, Barshaw Maternity Hospital, Paisley, and to the County of Renfrew; examiner to Glasgow University, the Royal Faculty of Physicians and Surgeons of Glasgow, the Central Midwives Board for Scotland, Edinburgh University, and the Royal College of Surgeons of Edinburgh. He had previously held appointments as visiting surgeon, Royal Maternity and Women's Hospital, Glasgow, and first assistant to the Regius Professor of Midwifery, Glasgow University. In 1931 McIntyre was elected a Foundation Member of the newly established College of Obstetricians and Gynaecologists, becoming a Fellow of the College in the following year. At the Annual Meeting of the British Medical Association held at Cambridge in 1948 he served as a vice-president of the Section of Obstetrics and Gynaecology. He wrote a number of monographs and was part author of *Operative Obstetrics* (1937) and *Combined Textbook of Obstetrics and Gynaecology* (1950). He had an extensive practice in Glasgow and

the west of Scotland, and his death will be mourned by thousands of his former patients. He is survived by a widow and son, to whom we extend our sympathy.—A. S.

Dr. ALBERT SHARMAN writes: Donald McIntyre will be sorely missed, not only by thousands of his former patients, but also by his professional colleagues. He served on numerous governing bodies, where his wise counsel was much appreciated. As a teacher, operator, and research worker he was first-class. A warm and generous host, he loved entertaining, revealing a charming and stimulating personality. In his younger days he enjoyed golf, but during his latter years he turned for recreation to yachting and lobster-fishing. One of his great joys was a trip to Murrayfield to watch an international rugby match, which he rarely missed. Several months ago he learned the nature of his illness, from which there could be no recovery. It was typical of him that he bore the death sentence with a fortitude beyond praise.

Dr. WILLIAM LAIRD writes: May I be permitted to record my appreciation of the late Dr. Donald McIntyre, who died at the age of 63 at a time when he was contemplating retirement from active work and the enjoyment of a well-earned rest? I had the pleasure of knowing him for over forty years, and during that period had ample opportunity of appreciating his sterling qualities. He was a man of high intellectual attainments, with an extensive knowledge of gynaecological literature, and he possessed operative dexterity and sound judgment. These qualities brought him many friends and patients. As a sportsman he was delightful, a good shot, a keen fisherman, and a steady golfer. He knew how to play a salmon, and it was a pleasure to watch him wield a rod. His ability to speak Gaelic smoothed away any difficulties that arose with the gillies on these fishing occasions. Rain, frost, sleet, fish not taking, birds not rising—none of these disturbed his equanimity. He took everything as it came, and the last time I saw him, two days before his death, I found the same serenity. The knowledge that he was dying did not disturb him and he was resigned to take the inevitable with a smile.

Dr. WILLIAM CLEMENT writes: As a former colleague of Dr. Donald McIntyre I would like to pay tribute to the great esteem and affection in which he was held by those who knew him. His great sense of duty, his scrupulous attention to detail, and his superb operative skill were an inspiration and example to those privileged to work with him. During working hours he was always serious and sometimes even stern, but to meet him socially revealed another side to his character. His love of life and sense of fun added gaiety to any party. To his recreations he gave the same wholehearted enthusiasm. Indeed, to all he did he gave all he had. His example to the end will be hard to follow.

Dr. R. J. WOTHERSPOON writes: Those of us who had the good fortune to train under Donald McIntyre cannot let the occasion of his death pass without recording our tribute to a great teacher. That he achieved his ends as a teacher mainly by example is a measure of his own devotion to his work, his attention to detail, and his clear thinking. We will long remember him for his loyalty to his profession and to himself and will regret his untimely death.

A. J. SLESSOR, M.V.O., M.B., F.R.C.S., F.R.C.S.Ed.

Mr. A. J. Slessor, surgeon to the Western General Hospital at Edinburgh, died in Edinburgh Royal Infirmary on October 17 at the age of 42.

Alexander Johnston Slessor was born on June 5, 1912, the son of the late Dr. T. S. Slessor, of Inverness, and was educated at Aberdeen Grammar School and at Aberdeen University, where he graduated M.B., Ch.B., with honours, in 1935. After graduation he held various appointments at Aberdeen Royal Infirmary, and gained the F.R.C.S.Ed. in 1938. He then spent a year in the Mayo Clinic and in visiting other surgical clinics in the United States and Canada with a Garden Fellowship awarded by Aberdeen University. He held the fellowship from 1938 to 1941, he and three others being the first to receive the award, which was founded under the will of Arthur William Garden for medical or surgical research. On his return to this country Mr. Slessor was appointed acting medical superintendent and assistant surgeon to the Western General Hospital at Edinburgh. In 1941 he became a Fellow of the Royal College of Surgeons of England.

During the early years of the last war he was closely associated with Professor J. R. (now Sir James) Learmonth in the work of the E.M.S. peripheral nerve and peripheral vascular injuries unit at Gogarburn, and the experience he gained there was put to valuable use when he entered the R.A.M.C. in 1943. Later he became officer in charge of a peripheral nerve injuries unit in South Africa and India, with the rank of lieutenant-colonel. After demobilization in 1946 he returned to Edinburgh University to work in the department of surgery and as clinical tutor in the professorial unit at the Royal Infirmary. In 1948 he was appointed assistant surgeon at the Western General Hospital, a post he held until his untimely death. For about four years he acted also as visiting consultant surgeon to the Royal Edinburgh Hospital for Mental and Nervous Disorders and to the City Infectious Diseases Hospital. He was an examiner for the Fellowship of the Royal College of Surgeons of Edinburgh.

In 1949, when the late King George VI was suffering from vascular disease of the leg, Mr. Slessor was one of the surgeons in attendance, and he acted as assistant surgeon to Sir James Learmonth when the King underwent the operation of lumbar sympathectomy in March of that year, and signed the bulletin. In recognition of these services he was appointed a Member of the Royal Victorian Order two months later. Mr. Slessor married Dr. Phyllis Davidson in 1940, and she survives him, together with a son and two daughters.

We are indebted to Mr. JOHN BRUCE for the following appreciation: Those of us who took our last farewell of Sandy Slessor at the simple and moving ceremony in Edinburgh will long carry in our hearts the remembrance of a quiet courage and a devotion to duty that was in very truth the triumph of the human spirit over the frailties of human flesh, for he had known for some time that he was mortally afflicted and that the number of his days was short. He accepted his fate without self-pity and without apparent resentment, and until a day or two before the end he gave to his work and his teaching the best that had always been his ideal and his practice. Perhaps—though this was scarcely possible—there was a gentler smile and a kindlier word for those who were stricken as he was, and to whom he was eager and anxious to impart some of his own resignation and his composure in the face of the last enemy. None of us who worked in intimate association with him during these last months but would willingly have eased his burden and shared his grievous load. We watched with anguish and with

humility a gradual sapping of his notable vitality and the almost reckless generosity with which he spent his ebbing strength. I know he saw through our clumsy attempts to spare him, but I know too that he was touched and comforted by our inarticulate sympathy.

His passing leaves the craft of surgery, his medical school, and his hospital the poorer, for Sandy Slessor's career held the promise of a great distinction. The worthy pupil of a great master, he had already established a formidable skill and an unquestioned authority in those branches of surgery that dealt with peripheral vascular disorders and the injuries of peripheral nerves. We were associates in India during the late war, and I came to know something of the thought, the skill, and the devotion he brought to the care of the victims of battle. It was all the rarer a privilege to welcome him again as a colleague after we both came home. And during the six years of our association I had come to appreciate his surgical wisdom, his intellectual integrity, and his judgment. As an operator, he was gentle and precise, confident but yet conservative, and his natural kindliness and his patience combined to create in his operating theatre a sense of the dignity of our craft that was both instructive and inspiring to the rest of us. To his teaching he brought the same standards of perfection and an understanding that endeared him to students and graduates alike.

Apart from his work, Sandy Slessor was the best of good companions. A shrewd sense of humour and a zest for life gave his social intimacies a charm and a gaiety that were memorable and precious, and his modesty made him the friend and the confidant of all. It was all the more tragic, as the sands of time were running out and he had to husband his vanishing physical resources, that he elected to forgo most of his social occasions and most of his leisure activities in order to preserve his energies for his work. But this was the measure of his quality and the hallmark of his essential goodness.

It was some consolation to know, as we all did, that at the fireside to which he returned, as day followed day, with the weary burden of increasing weakness he found a courage as faultless as his own, and a help that must have sustained him and comforted him as the shadows began to lengthen. To her who gave him so much, and to his three young children, our deepest sympathy goes out.

And so we salute Sandy Slessor for the last time. We are all grateful for his genial companionship no less than for his loyalty and his surgical wisdom. It would have been a privilege to have been allowed to show him more of our great affection for him as the tale of his days was nearly told, but mercifully the end came quickly, and we who mourn him thank God for a life of service lived well and ended with a nobility that will inspire and uplift us when our own time draws near. "When he passed over," John Bunyan wrote of Mr. Greatheart, "the trumpets sounded on the other side." I can think of no better postscript to the brief chapter of Sandy Slessor's brave and splendid years.

G. R. JEFFREY, M.D., F.R.C.P.Ed.

Dr. G. R. Jeffrey, who was medical superintendent of Bootham Park, York, for twenty-five years, died at his home in London on October 13 at the age of 75.

A native of Jedburgh, where his father, Dr. William Jeffrey, was in general practice, George Rutherford Jeffrey was born on December 9, 1878. After receiving his early education at Jedburgh and Edinburgh Academies, he enrolled at the Edinburgh New School of Medicine and later entered Glasgow University, where he graduated M.B., Ch.B. in 1902, gaining distinctions in materia medica, surgery, and clinical surgery. Elected M.R.C.P.Ed. in 1908, he became a Fellow three years later, and proceeded to the M.D. in 1909. He was elected a Fellow of the Royal Society of Edinburgh in 1912.

After graduation Jeffrey held the appointment of house-surgeon at the Western Infirmary, Glasgow, but an early interest in psychiatry, which he studied in Vienna, led him to seek appointments at Edinburgh Royal Asylum and Ayr District Asylum. In 1906 he became senior assistant physician at Crichton Royal Infirmary, Dumfries, where he was appointed interim physician-superintendent in the following year. His work at Bootham Park began in 1912, when he was selected as medical superintendent. He was then 33 years of age, scholarly, cultured, and possessing a sure human touch. He quickly proceeded to build up a consulting practice in York and its environs. The impact on patients of his strong personality was a most powerful therapeutic weapon. His book, *Common Symptoms of the Unsound Mind*, published in 1923, illustrated his powers of observation, clarity of thought, and command of descriptive language. His administration of Bootham Park was as sound and as successful as the stringencies of the times would allow, for after two years war broke out and within a short time Jeffrey was serving in the R.A.M.C. Later, ill-health dogged his steps and ultimately caused his premature retirement in 1937.

Those who best knew Jeffrey will recall a gentleman of singular attraction and outstanding gifts. The zenith of his powers found him to be a general physician of more than average ability, an astute clinical psychiatrist, and a strong leader. He leaves a widow and a son, also a doctor, to whom our sympathy is extended.—D. R.

ALFRED COX, O.B.E., M.A., LL.D., M.B.

W. S. writes: As a layman I may perhaps be permitted to add another tribute to the memory of Dr. Alfred Cox. In the early 1920's Dr. Cox lived at Coulsdon, Surrey. Even though he was burdened with work, which in those years was particularly heavy because of negotiations under the Insurance Act, he found time to be not only a member but the moving spirit of a local debating society. Those who had the good fortune to meet him there will always recall his kindly, helpful, and critical contribution to the debates. It was good to have known him.

Dr. H. J. WESTON, who was in general practice at St. Leonards-on-Sea for over 40 years, died at his home at Sedlescombe, Sussex, on September 28 at the age of 83. Born on July 21, 1871, Henry James Weston qualified M.R.C.S., L.R.C.P. from St. Bartholomew's Hospital in 1900. He then held the appointments of assistant medical officer at St. Mary's Infirmary, Highgate Hill, and senior assistant medical officer at Lewisham Infirmary before leaving London in 1904 to settle in practice at St. Leonards, where he remained until he retired in 1946—except for two years spent at Redhill, Surrey, during the last war after his home at St. Leonards had been destroyed in an air raid. Nearly all the time he was in St. Leonards he acted as honorary medical officer to the Railway Convalescent Home there, and for many years he gave his services in a similar way to other institutions in the town. During the first world war he became honorary medical officer to the Beau Site Convalescent Home at Hastings. When he retired from practice soon after the end of the last war he went to live at Sedlescombe, near Battle. A member of the British Medical Association for over 40 years, he was usually to be seen at meetings of the local Division until shortly before his death. He was also a member of many years' standing of the East Sussex Medico-Chirurgical Society. Dr. Weston was well known and respected in Hastings and St. Leonards and was a staunch supporter of the parish church of St. Leonards, where many of the senior members of the medical profession attended his funeral service.

Medico-Legal

SERVANTS OF THE MINISTER

In an action for negligence brought by Mrs. G. M. Razzel, of Eastbourne, against Mr. L. A. H. Snowball, part-time consultant orthopaedic surgeon at St. Mary's Hospital, Eastbourne, the defendant surgeon not only denied negligence but pleaded that the action was barred by the Limitation Act, 1939, since it was not begun within a year. In the Court of Appeal on October 25 the surgeon's case was upheld.[1]

In his judgment Lord Justice Denning said that the defendant relied on the National Health Service Act, 1946, under which it was the Minister's duty to provide the services of specialists. When operating, they were only the servants of the Minister and were protected by the Act. The plaintiff's argument was that the only duty of the Minister was to provide the specialists themselves and not their services. Lord Justice Denning's view was that the surgeon, when performing his duties under his contract of part-time employment at a fixed rate of payment, was performing them as the servant or agent of the Minister. "Consultant" was now not a term which denoted a particular relationship between a doctor and a hospital, but was simply a title or grading denoting his place in the hierarchy of the hospital staff.

Lords Justice Birkett and Morris concurred.

The Limitation Act, 1939, required actions to be brought against "public authorities" within one year. Mr. Justice Pilcher earlier this year held[2] that a part-time specialist in a National Health Service hospital was covered by it. As Lord Justice Denning pointed out,[3] the question will not arise in future because the Law Reform (Limitation of Actions, etc.) Act, 1954, makes the period of limitation the same for everybody, whether public authority or not—namely, three years.

The Medical Defence Union instructed Messrs. Hempsons, solicitors, to act for Mr. Snowball.

PNEUMONIA CAUSED BY WORKING CONDITIONS

[From Our Medico-Legal Correspondent]

By the common law of England it has always been an employer's duty to take reasonable care for the safety of his servants; for a breach of this duty the servant can bring an action for damages.

In the conditions of the Industrial Revolution this did not adequately protect the workman who was in no position financially to embark on litigation, and the Factories Acts and the regulations made under the powers conferred by them created a code of precise obligations by the employer towards his workmen. The code is enforced by the inspectors of factories, and the breach of it was made a criminal offence. For breaches of these statutory duties the workman can also bring an action for damages against his employers which is really on all fours with the common law action except that what amounts to taking reasonable care for the workman is defined by the precise statutory obligation.

Among the regulations now in force are the Cellulose Solutions Regulations, 1934, which require extracting ventilation in spraying-rooms. In September, 1952, Walnut Cabinet Works Ltd. opened a new polishing shop and spraying-room at their premises in Vyner Street, Cambridge Heath, London, which was accordingly provided with ventilators and an extractor fan. Unfortunately, although the plans were ready for heating apparatus to meet the requirement of s. 3 of the Factories Act, 1937, that effective provision be made for securing and maintaining a reasonable temperature in each workroom in a factory, installation had been delayed.

Mr. James Murray was employed in the polishing shop during October. To get the proper light for his job he had to work in the air-stream between the ventilators and the extractor fan. He had always had good health and had been a distinguished amateur boxer, but although the weather was not severe during the period, with a minimum temperature of 41° F. (5° C.) recorded at the Meteorological Office, he complained of the cold and draughty conditions in which he had to work.

He was told it would be better when the heating was on, but on November 7, before the apparatus was installed, Mr. Murray fell ill with pneumonia and pleurisy. He brought an action[4] for damages against his employers for breach of their common law duty and their statutory duty; it was tried by Mr. Justice Cassels in the Queen's Bench Division on October 18. The Judge found that Mr. Murray's illness was caused by working in the forced circulation of cold air, which was a breach by the employers of both their common law and their statutory duty. In addition to special damages amounting to £101 18s. 6d. he awarded Mr. Murray £300.

A stay of execution was granted pending an appeal being considered.

[1] *The Times*, October 26.
[2] *British Medical Journal*, February 6, p. 341.
[3] *The Times*, October 26.
[4] Ibid., October 19.

Medical Notes in Parliament

Cancer Registration and Treatment

When Parliament reassembled on October 19 Mr. Norman Dodds (Dartford, Lab.) put a question to the Minister of Health asking what was the result of his request to hospitals to make greater efforts to achieve the registration of all cancer cases. Mr. Iain Macleod, replying on October 21, stated that the results had been generally encouraging, and he was satisfied that boards were doing their best. Progress depended largely on the co-operation of medical staffs, and also of general practitioners and medical officers of health for non-hospital cases, and boards were attempting to secure this. A number of hospitals had agreed to take part for the first time. Three more hospital regions had decided to set up central registration bureaux to collect records from all hospitals in the region and to stimulate hospitals to improve the standard of record-keeping.

Health Service Offences

Mr. W. Hamilton (Fife, West, Lab.) asked the Secretary of State for Scotland how many doctors and dentists had been found guilty of offences within the Health Service in each of the past five years, and whether he would ensure that full publicity was given to the names of such offenders. Mr. J. Stuart stated on October 19 that since July, 1948, two doctors and four dentists in Scotland had been excluded from practice in the Health Service. Sums of money had been withheld from remuneration on 44 occasions involving 43 doctors, and on 148 occasions involving 92 dentists, in respect of breaches of their terms of service. Full publicity was given to cases involving exclusion from practice, but it would not as a rule be fair to the practitioner or in the public interest to publish names in other cases.

Mr. Hamilton asked if there was any good reason why the name of a doctor or dentist who was in effect sabotaging the Health Service ought not to be given full publicity. Mr. Stuart said that if confidence in a doctor or dentist was not retained he was excluded from the Service and the name was published, but he did not think it would be right to do that in other cases, because it would destroy confidence in the practitioner.

Scottish Doctors' Surgeries

Mr. HAMILTON also asked the Secretary of State for Scotland how many complaints had come to his notice in the last year concerning unsatisfactory conditions in doctors' surgeries, and what was being done to improve the situation. Mr. STUART replied that he had received one such complaint. The representatives of the medical profession were themselves anxious to ensure high standards in accommodation, and he was discussing with them arrangements for a general survey of consulting-rooms so that improvements might be made where necessary.

Tuberculosis in Service Recruits

Mr. HAROLD WATKINSON, Parliamentary Secretary, Ministry of Labour and National Service, informed Mr. SOMERVILLE HASTINGS (Barking, Lab.) on October 19 that in 1952 71% and in 1953 78% of the men medically examined for national service were examined by mass radiography. Mr. HASTINGS asked whether, in view of the large number of cases of tuberculosis apparently contracted during national service, the Minister would consider the examination of all recruits by mass radiography within a very short time after they joined. Mr. WATKINSON replied that in the first three quarters of this year the percentage had gone up to just over 80, and it was hoped to get it higher still.

Mr. HAROLD MACMILLAN, Minister of Defence, stated in an answer to Mr. HASTINGS on October 20 that in 1952 and in 1953 about one recruit in 1,000 was found to have developed tuberculosis of the lung during his period of national service.

Colonial Medical Service

Mr. A. LENNOX-BOYD, Secretary of State for the Colonies, stated in answer to Mr. V. YATES (Birmingham, Ladywood, Lab.) on October 20 that the total number of doctors in the colonies and protectorates was approximately 6,000, including those who did not hold fully registrable qualifications but were licensed to practise. This represented an average of 12,500 people for each practitioner for the colonies and protectorates as a whole.

Horror Comics

Mr. J. RANKIN (Tradeston, Lab.) asked on October 21 whether the Home Secretary's attention had been directed to the nature of American children's comics now being sold in this country; if he was aware that they had a demoralizing effect on the minds of children, because they helped to spread illiteracy and encourage sadistic practices; and if he would take steps to prevent their circulation among children. Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.), Mr. B. JANNER (Leicester, North-West, Lab.), and Mr. M. ORBACH (Willesden, East, Lab.), asked similar questions. The Home Secretary, Major LLOYD GEORGE, said he was aware of public concern about this matter, to which he was giving very careful consideration.

Mr. RANKIN asked if he would consider whether these products could be banned from this country, or, if that was impossible, would he try to find a definition of "obscenity" which would bring them within the law. Major LLOYD GEORGE pointed out that the definition required was not an easy matter, nor was it easy to differentiate between what was objectionable and what was not. Dr. STROSS said that some newsagents did not want to handle this rather beastly material and looked to the Home Secretary for assistance. Major LLOYD GEORGE replied that they also had some responsibility in the matter. "If they feel that they do not want to handle the material, I should have thought that the best thing was for them not to handle it." There was also the responsibility of parents and teachers. Major LLOYD GEORGE assured the House that he would do everything he could.

In reply to a later question from Mr. K. ROBINSON (St. Pancras, North, Lab.) asking the Home Secretary to amend the law relating to obscenity in literature, Major LLOYD GEORGE said he proposed to look into the problem as soon as possible.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 9** (No. 40) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	15	0	7	0		25	1	5	1	
Dysentery	438	51	182	3		202	30	94	4	4
Encephalitis, acute	1	0		0		4	0	1	0	
Enteric fever:										
Typhoid	7	0	1	0		6	0	0	0	
Paratyphoid	7	2	1 (B)	0		8	1	2 (B)	0	1 (B)
Food-poisoning	230	24		10		280	88		1	
Infective enteritis or diarrhoea under 2 years				19	10				14	73
Measles*	2,358	159	305	42	179	608	16	59	16	24
Meningococcal infection	20	3	11	1		12	1	14		1
Ophthalmia neonatorum	31	1	10	0		27	5	11	0	
Pneumonia†	355	20	132	3	1	206	13	109	7	
Poliomyelitis, acute:										
Paralytic	45	1	31	3	2	123	13	14	18	10
Non-paralytic	27	0				104	9			
Puerperal fever§	244	43	13	0		251	42	11	2	
Scarlet fever	681	56	125	19	33	633	29	153	20	38
Tuberculosis:										
Respiratory	661	75	102	19				135	22	
Non-respiratory	93	7	16	6				21	6	
Whooping-cough	1,276	64	115	16	17	3,555	281	313	21	42

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	1	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	2	0		0	1	9	1	0	2	1
Influenza	4	0	0	0	0	1	0	0	0	0
Measles		0	1	0	0		0	0	0	0
Meningococcal infection		1	0				1	0		
Pneumonia	161	29		8	4	116	20	13	8	5
Poliomyelitis, acute	0	0			0	2	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	79	8		3	8	83	6	9	2	3
Non-respiratory		2		1	2		2	2	0	2
Whooping-cough	1	0	0	0	0	1	0	2	0	
Deaths 0–1 year	208	28	34	6	9	174	22	20	6	18
Deaths (excluding stillbirths)	4,758	707	593	117	151	4,236	606	496	85	128
LIVE BIRTHS	7,671	1149	963	225	424	7,010	1019	820	233	390
STILLBIRTHS	177	26	20			171	28	19		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

No Atomic Waste in Forest of Dean

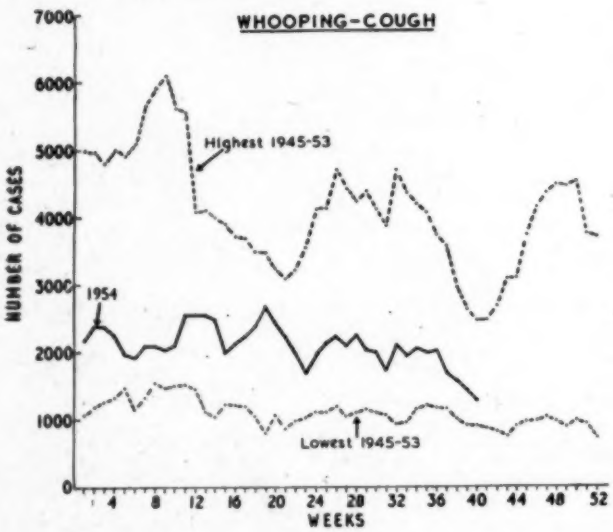
The Atomic Energy Authority will not, after all, dispose of atomic waste in the Forest of Dean mines.[1] Six weeks ago Sir John Cockcroft and other Harwell research workers addressed local representatives in the area,[2] and it seemed that the public health aspects were satisfactory. The scheme is reported to have been withdrawn now because of the opposition of the Freeminers of the Forest. These are natives of the Forest of Dean who have each worked a year and a day down a coal mine and after complying with certain formalities have obtained privileges to work seams of coal in spite of nationalization.

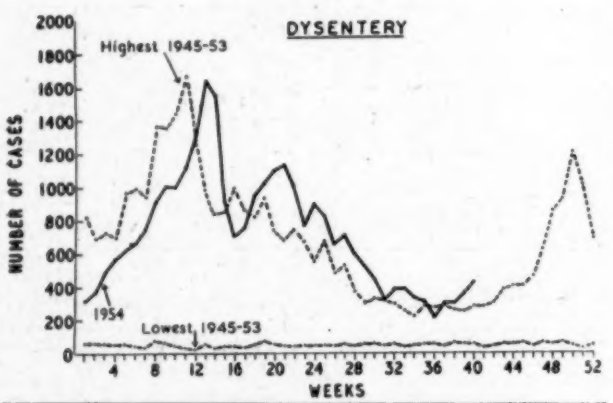
Week Ending October 16

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 777, whooping-cough 1,393, diphtheria 13, measles 2,801, acute pneumonia 346, acute poliomyelitis 71, dysentery 507, paratyphoid fever 9, and typhoid fever 8.

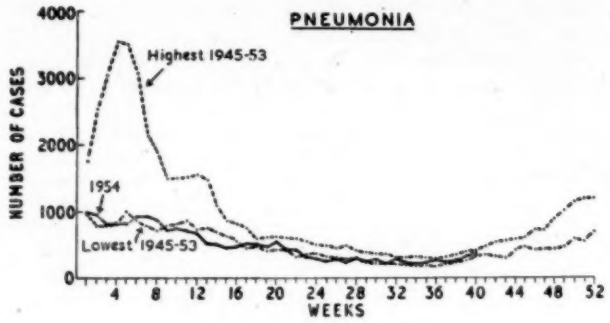
Graphs of Infectious Diseases

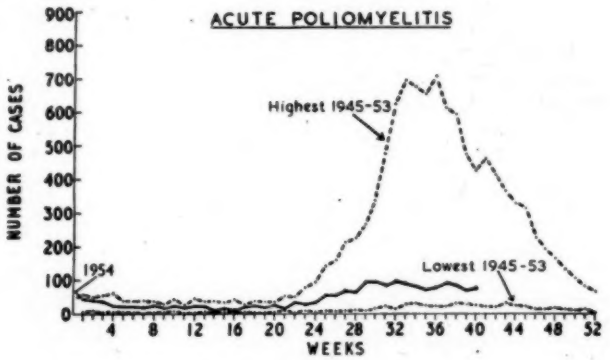
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ———. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





[1] *The Times*, October 20.
[2] *British Medical Journal*, September 25, p. 761.





Infectious Diseases

The largest variations in the incidence of infectious diseases in England and Wales during the week ending October 9 were increases in the number of notifications of 525 for measles, from 1,833 to 2,358, 135 for scarlet fever, from 546 to 681, and 69 for dysentery, from 369 to 438, and the only large decrease was 188 for whooping-cough, from 1,464 to 1,276.

The largest rises in the local trends of measles were 338 in Lancashire, from 732 to 1,070, and 51 in Derbyshire, from 55 to 106. A small rise in the incidence of scarlet fever occurred in most regions, but no large fluctuations in trends were recorded. The largest falls in the notifications of whooping-cough were 51 in Durham, from 112 to 61, 47 in Warwickshire, from 83 to 36, and 40 in Kent, from 112 to 72. 15 cases of diphtheria were notified, being 4 more than in the preceding week. The chief feature of the returns of diphtheria was a rise in Birmingham C.B. from 0 to 6. The other areas with multiple cases of diphtheria were Lancashire, Liverpool C.B. 4, and Middlesex, Hornsey M.B. 2.

72 cases of acute poliomyelitis were notified, and these were 1 fewer for paralytic and 3 more for non-paralytic cases than in the preceding week. The largest returns were Lancashire 10 (Liverpool C.B. 2, Accrington M.B. 2), Durham 9 (Gateshead C.B. 2, Chester-le-Street R.D. 2), Essex 7 (Brightlingsea U.D. 3), Derbyshire 5 (Long Eaton U.D. 2, Ripley U.D. 2), Yorkshire East Riding 5 (Kingston-upon-Hull C.B. 3).

In Scotland the notifications of acute poliomyelitis rose from 15 to 31. 14 cases were notified in the north-eastern region and 7 in the south-eastern and in the western regions.

The largest centres of dysentery were Yorkshire West Riding 79 (Wetherby R.D. 19, Sheffield C.B. 18, Leeds C.B. 16, Featherstone U.D. 11), London 51 (Islington 14), Lancashire 45 (Liverpool C.B. 16, Manchester C.B. 11), Middlesex 43 (Edmonton M.B. 32), Lincolnshire 32 (Barton-upon-Humber U.D. 21), and Southampton County 17 (Droxford R.D. 12).

September Quarter in England and Wales

Live births registered were 167,070, representing a rate of 15.0 per 1,000 population, compared with 15.6 for the 1953 and 15.2 for the 1952 third quarters. 104,112 deaths

were registered, representing a rate of 9.4 per 1,000 population, compared with 8.9 in the third quarter of 1953 and 8.9 in the third quarter of 1952. Deaths of children under 1 year of age numbered 3,530, giving a record low rate for a September quarter of 21.0 per 1,000 related live births, compared with 22.2 in the corresponding quarter of 1953. In the third quarter of 1938 the corresponding rate was 42.5. There were 3,918 stillbirths registered, giving a rate of 22.9 per 1,000 total live and stillbirths, compared with 21.0 in the corresponding quarter of 1953. The rate for the third quarter of 1938 was 37.0.

Medical News

Royal Visit to Liverpool.—The Queen and the Duke of Edinburgh visited the Liverpool School of Tropical Medicine on the afternoon of October 21, following a switch of plans arising from the dock strike. Senior members of the staff and their wives were presented to the Queen by the vice-chairman, Mr. Leslie Harding, and to the Duke by the Dean, Professor B. G. Maegraith. Her Majesty and the Duke spent nearly an hour in the School, watching demonstrations of its research work and activities. Before leaving they signed the Distinguished Visitors Book.

The President's Health Programme.—Speaking at a dinner in New York on October 21, President Eisenhower is reported to have stated his intention of resubmitting his health insurance programme to Congress as "the logical alternative to socialized medicine." The programme, which aims to encourage voluntary health insurance, was defeated last July in Congress by 238 votes to 134. According to the *New York Times*, Representative Charles Wolverton, the bill's sponsor, blamed the American Medical Association for its defeat. The Administration had contended that the programme would have made voluntary health insurance available to 63 million Americans not now covered, and broadened the cover for 92 million others already insured.

British Postgraduate Medical Federation Lectures.—On October 19 Professor A. V. Hill, C.H., F.R.S., delivered in London the inaugural lecture of the Federation's winter series of 30 lectures on "The Scientific Basis of Medicine." He took as his subject "Why Biophysics?" and asked what role this new branch of science could play in medical progress and practice. One advantage of such a borderland subject, as was the case with biochemistry, was that it might provide room for people whose special knowledge or talents could not fit into the accepted scheme, said Professor Hill. Especially since the war, an important number of young physicists were seeing a fruitful outlet for physical ideas and methods in biology. This did not mean a divorce from chemistry; most vital processes took place in an aqueous medium in which chemists were much more at home than physicists, and biophysics without physical chemistry as an essential part of its make-up would have little reason for a separate existence. Radiobiology, or the study of the effects of radiation on tissues, was an important aspect of biophysics; another was the study of the minute structure of living cells. A biophysicist needed the intuitions and experience of both the physicist and the biologist, in addition to technical and theoretical proficiency. The use of the latest physical methods and devices did not make one a physicist; nor was their use in a biological laboratory necessarily biophysics. "In every field of medical science and of medicine," declared Professor Hill, "we are witnessing the impact of chemistry and physics: on ways of looking at things, on research, on diagnosis and treatment. Indeed, the very nature of our modern society, based as it is on engineering application of the physical sciences, is bringing a host of new problems to human biology and medicine." The lectures in this series will eventually be published as a book by the Athlone Press.

Local Authorities and the Hospital Service.—The West Riding County Council last week approved a resolution from its law and parliamentary committee wholly opposing the return of any part of the hospital service to local authorities (*Yorkshire Post*, October 21). The committee had earlier considered a memorandum on local government reorganization from the County Councils Association, which recommended (1) that "more responsibility can be and should be given to local authorities" in the administration of hospitals, and (2) that "the assumption by the local health authority of the function of executive councils, with appropriate representation of medical, dental, and pharmaceutical interests should be the aim." The committee took the view that to bring forward proposals of such a revolutionary character at this stage would be contrary to all accepted principles of good government.

Exchange Visit to the U.S.A.—Applications are invited for a casual vacancy which has arisen in the scheme for exchange visits between members of the American and British Medical Associations during the current financial year. The successful applicant will be able to deposit up to £200 with the B.M.A. and to draw the equivalent in dollars on his arrival in the U.S.A. He will be required to make his own travel arrangements, and should begin his journey on or before March 31, 1955. Medical practitioners in all branches of the profession are eligible. Applications, including a statement of the object of the visit, must reach the Secretary of the B.M.A. not later than November 29.

London School of Hygiene and Tropical Medicine Association.—The annual dinner was held on October 22 at the Holborn Restaurant and was, as usual, exemplary for the brevity of the speeches and the conviviality of the diners. The dean, Dr. Andrew Topping, introduced the speakers, felicitously imposing a time limit of three minutes on each. Sir Archibald Gray, chairman of the board of management, proposed the toast to the School, and in reply Sir Wilson Jameson observed it was 25 years ago that the work of the School began in its new building in Keppel Street. Mr. Graham Don proposed the health of the guests.

NOBEL PRIZE WINNERS

(See *Annotation*, p. 1041)

Dr. T. H. Weller. Dr. J. F. Enders. Dr. F. C. Robbins.

[Associated Press Photo

Royal College of Obstetricians and Gynaecologists.—The London County Council has lost its appeal against the siting of the new college on Crown land in Regent's Park (see *British Medical Journal*, September 25, p. 749). The L.C.C. wanted to use the site for flats. The Minister of Housing and Local Government has informed the R.C.O.G. that they may now proceed with their plans.

Australian Ophthalmology Prize.—The Ophthalmological Society of New South Wales invites applications for its Norman McAlister Gregg triennial prize. The prize of 100 guineas and a bronze medallion will be awarded to the British subject whose work is considered the most valuable contribution to knowledge in ophthalmology. The closing date for entries is August 31, 1955. Intending candidates should notify the secretary of the society (Dr. E. J. Donaldson, 229, Macquarie Street, Sydney) at least two months before the closing date.

Christmas Cards and Seals.—Both the United Nations Children's Fund (U.N.I.C.E.F.) and the National Association for the Prevention of Tuberculosis (N.A.P.T.) are again selling Christmas cards for their funds, and the latter also Christmas seals. U.N.I.C.E.F. offers boxes of 10 cards in five designs (that is, two of each) showing children from different countries enjoying themselves. The boxes, with envelopes, cost 7s. 6d. each and may be obtained from the U.N.I.C.E.F. Greeting Card Fund, Clive House (7th Floor), Petty France, London, S.W.1. Last year over two million cards were sold (320,000 in Britain), making a profit of £34,000. Sets of last year's cards are also available. N.A.P.T. has chosen the theme "Holly and Candles" for its appeal, and this is the design on the gaily coloured seals and on one of the cards; the other card is of a coach and horses. The seals, of which 100 million are being issued, cost 4s. a sheet of 100, the coloured cards to match 8s. a dozen, and the black-and-white cards with the coach 4s. a dozen. Seals and cards may be obtained from N.A.P.T., Tavistock House North, Tavistock Square, London, W.C.1.

Tobacco Again.—Last week in the United States tobacco hit the headlines on three fronts. First came a report that tars from cigarette papers had caused skin cancers in mice. This was followed closely by a statement from the board of the American Cancer Society drawing the public's attention to the dangers of cardiovascular damage from cigarette smoking. And finally the American tobacco industry research committee announced its research programme. Two of the more interesting lines of investigation are a geographical and occupational study of the incidence of lung cancer and an investigation of the emotional make-up of smokers. Other studies include the preparation and analysis of tobacco derivatives and their application to animals, experimental investigation of the inhalation of smoke, and the study of lung cancer in various medical centres.

British Medical Films for International Congress.—The following British medical films will be shown at the Eighth International Scientific Film Congress in Rome next month (November 6–12): "Tubegauz" (G.B. Specialized Film Unit—The Scholl Manufacturing Co. Ltd.); "Dissection of a Mosquito" (Wellcome Film Unit); "Sensitivity to Antibiotic Injections" (Basic—Central Office of Information); "Streamline Flow in Veins" (Wellcome Film Unit); "Conjoined Twins of Kano" (Stanley Schofield Productions Ltd.); "Hydrocolloids and Their Use in Operative Dental Surgery" (D. N. Allan); and "Urine Analysis for Diabetics" (Eothen Films Ltd.).

News in Brief.—Professor Wilder Penfield, O.M., F.R.S., director of the Montreal Neurological Institute, will receive the honorary D.Sc. of Leeds University on November 5.

The Monopolies and Restrictive Practices Commission has appointed a group, under the chairmanship of Mr. D. A. S. Cairns, Q.C., to report to it on the supply of certain industrial and medical gases.

Professor Walter Mercer was re-elected president, and Professor R. C. Alexander and Mr. John Bruce were re-elected vice-presidents, of the Royal College of Surgeons of Edinburgh at the annual meeting on October 20.

Dr. E. T. Freeman was re-elected president, and Dr. D. M. Mitchell was elected vice-president, of the Royal College of Physicians of Ireland at the annual meeting on St. Luke's Day.

At the opening meeting of the 118th session of the Liverpool Medical Institution on October 14 a presentation was made to the resident librarian, Mr. W. A. Lee, and Mrs. Lee, in recognition of their 25 years' service to the Institution. Afterwards Sir Henry Cohen, the president, gave an address on "Old English Silver and its Medical Interest."

The Derby Medical Society has presented a George II loving-cup to the County Borough of Derby on the occasion of the Borough's octocentenary. The presentation was made by Dr. E. C. Dawson, the society's president.

Dr. Andrew Topping, dean of the London School of Hygiene and Tropical Medicine, has been elected an honorary fellow of the American Public Health Association.

Bayer Products Ltd. have moved their administrative headquarters (including the medical information department) to Neville House, Eden Street, Kingston-on-Thames, Surrey (telephone, Kingston 7733).

COMING EVENTS

War Memorial.—The Archbishop of Canterbury will dedicate the War Memorial at B.M.A. House on November 2 at 3 p.m. For details see *Journal*, October 9, p. 882. Ticket-holders are reminded that the main entrance gates of B.M.A. House will be closed from noon onwards. Cars should be parked in neighbouring squares, as after noon access to the garage will not be possible.

Bradshaw Lecture.—Dr. F. H. K. Green will lecture on "The Clinical Evaluation of Remedies" at the Royal College of Physicians on November 11 at 5 p.m.

Manchester Medical Students' Ball.—On November 12 at the Whitworth Hall, 8 p.m.–2 a.m. One guinea for double ticket. Apply social secretary, Medical Students' Representative Council, Medical School, The University, Manchester, 13.

Medical Women's Federation.—On November 12 and 13 (9.30 a.m.) council meeting of London Association at B.M.A. House. All members of Federation welcome as observers. The council dinner is on November 12 at the Royal College of Surgeons. Some additional tickets are available (£2 5s.) from hon. treasurer, London Association, before October 30.

British Medical Students' Association.—Thirteenth annual general meeting at B.M.A. House on November 12, 13, and 14. The meeting will be opened by Lord Horder and addressed by the Minister of Health.

Royal Air Force Medical and Dental Services.—24th annual dinner, November 12, at the Hyde Park Hotel. Tickets 27s. 6d. from the secretary (Air Ministry, M.A. 3), Awdry House, Kingsway, London, W.C.2.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, October 30

Kent Paediatric and Child Health Society.—At West Kent General Hospital, Marsham Street, Maidstone, 3 p.m., clinical meeting.

Monday, November 1

●Institute of Neurology.—5.30 p.m., Dr. E. A. Blake Pritchard: Pupillary Abnormalities.

Institute of Psychiatry.—5.30 p.m., lecture demonstration by Dr. E. Stengel.

Tuesday, November 2

British Postgraduate Medical Federation.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. P. M. Daniel: Some Features of the Peripheral Circulation and Vascular Bed.

●Institute of Obstetrics and Gynaecology.—At Chelsea Hospital for Women, 4.30 p.m., Mr. D. Fraser: Treatment of Endometriosis.

King's College Hospital Medical School.—5 p.m., 3rd Dorothy Platt Memorial Lecture by Professor Geoffrey Hadfield: Co-Carcinogenesis.

Royal College of Surgeons of England.—5 p.m., Arris and Gale Lecture by Dr. B. D. Wyke: Cortical Control of Movement: A Contribution to the Surgical Physiology of Seizures.

St. Mary's Hospital Medical School.—5 p.m., Mr. J. A. Stallworthy: Infertility.

SOCIETY OF APOTHECARIES OF LONDON.—4.30 p.m., Dr. E. F. Scowen: Clinico-pathological Aspect of Bilateral Adrenalectomy; 5.45 p.m., Mr. J. D. Fergusson: Surgical Aspect of Bilateral Adrenalectomy.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., neurological demonstration by Dr. C. C. Edwards.

Wednesday, November 3

EDINBURGH CLINICAL CLUB.—4 p.m., visit to Princess Margaret Rose Hospital for Crippled Children.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Diagnosis of Ringworm Infection.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professor F. C. Ormerod: Sigmoid Sinus Thrombosis.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. Harland Rees: Differential Diagnosis of Frequency of Micturition.
MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 154, Great Charles Street, 8.15 p.m., Dr. J. H. Sheldon: Old Age.
PHARMACEUTICAL SOCIETY: NORWICH BRANCH.—At Assembly House, Theatre Street, Norwich, 7.30 p.m., Dr. E. Lester Smith: Isolation, Properties, and Functions of the Vitamins B_{12}. (Illustrated by lantern slides.) Members of the Norwich Division of the B.M.A. are invited.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor R. H. S. Thompson: Biochemical Investigations in Nervous Disorders.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. R. I. Mackay: Headache in Childhood (Illustrated).

Thursday, November 4

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor W. T. J. Morgan, F.R.S.: Chemical Basis of Blood Group Specificity in Man.
FACULTY OF ANAESTHETISTS: ROYAL COLLEGE OF SURGEONS OF ENGLAND.—4.30 p.m., Frederic Hewitt Lecture by Dr. H. J. V. Morton: Education and Recreation in Routine Work.
FACULTY OF HOMOEOPATHY.—5 p.m., Dr. Kathleen G. Priestman: Homoeopathic Case-taking in Children.
GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY.—At Glasgow University Union, 7.30 p.m., Professor G. M. Wyburn: The New Anatomy.
HONYMAN GILLESPIE LECTURE.—At University New Buildings, Edinburgh, 5 p.m., Dr. Donald Stewart: Industrial Rehabilitation.
LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Dr. W. N. Pickles: Epidemiology in Country Practice.
LONDON UNIVERSITY.—At Royal Society of Medicine, 5 p.m., Semon Lecture by Professor Eelco Huizinga (Groningen): Bronchological Pneumonology.
RESEARCH DEFENCE SOCIETY.—At Physiology Lecture Theatre, University College, 5.30 p.m., 23rd Stephen Paget Memorial Lecture by Sir Geoffrey Jefferson, F.R.S.: Man as an Experimental Animal.
ROYAL EYE HOSPITAL.—5.30 p.m., Dr. T. H. Whittington: Myopia, and the Care and Treatment of the Myopic Patient.
ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION.—At Royal Society of Medicine, 2.15 p.m., 29th Maudsley Lecture by Professor Wilder Penfield, O.M., F.R.S.: Role of the Temporal Cortex in Certain Psychical Phenomena.
ST. ANDREW'S UNIVERSITY.—At Physiology Department, Medical School, Small's Wynd, Dundee, 5 p.m., Professor A. J. Lewis: Trends in Psychiatry.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. D. J. Williams: Neurology demonstration.
SOCIETY OF APOTHECARIES OF LONDON.—4.30 p.m., Professor L. P. Garrod: Some Recent Developments in Antibiotic Therapy; 5.45 p.m., Sir Lionel Whitby: Treatment of Anaemia.

Friday, November 5

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. R. M. B. MacKenna.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Mr. W. P. Cleland.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 2 p.m., Professor P. A. Fitzgerald: Investigation and Treatment of Lower Limb Venous Insufficiency. (2) 4 p.m., Dr. D. J. Williams.
●ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Mr. Kenneth Fraser: Surgery in Pulmonary Tuberculosis.

Saturday, November 6

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—11.30 a.m., Professor Eelco Huizinga (Groningen): Physiological and Clinical Importance of Experimental Work on the Pigeon's Labyrinth.
MIDLAND TUBERCULOSIS SOCIETY.—At Birmingham Chest Clinic, 3 p.m., Professor J. Gough: Correlation of Radiology and Pathology in Some Diseases of the Lung.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Hammar.—On October 16, 1954, at the Charing Cross Hospital, London, W.C., to Berenice, wife of Dr. B. Hammar, a son—Paul David.
Mills.—On October 6, 1954, to Sheila I. (formerly Haldane), M.B., Ch.B., wife of Robert B. Mills, B.Sc., A.H.-W.C., A.R.I.C., of 2, Lyndhurst Road, Corringham, Essex, a daughter.

MARRIAGES

McHugh—McGlinchey.—On September 18, 1954, at St. Teresa's Church, Cleveleys, Lancs, Dr. John McHugh, D.P.H., to Dr. Alice T. McGlinchey, D.C.H., D.P.H.

DEATHS

Gelber.—On October 3, 1954, at the Central Middlesex Hospital, London, N.W., Ludwik George Gelber, M.B., Ch.B., of Tunbridge Wells, Kent, aged 37.
Johnston.—On October 2, 1954, at the home of his son, 1A, Inverleith Row, Edinburgh, Samuel Everett Johnston, M.B., C.M., late of Penpont, Dumfriesshire.
Langwill.—On September 29, 1954, James Langwill, M.D., of 8, Lussielaw Road, Edinburgh, formerly of Kirkcaldy, Fife.
O'Rorke.—On September 25, 1954, Charles Hyacinth O'Rorke, M.B., B.Ch., Major, R.A.M.C., retired, of Oaklands, Dawlish Warren, South Devon.
Paxton.—On September 30, 1954, John Paxton, L.R.C.P.&S.Ed., L.R.F.P.S., of 2, White Buildings, Lee-on-Solent, Hants, late of Yacht "Helbe."
Scargill.—On October 3, 1954, in a nursing-home, Leeds, Harold Brooke Scargill M.B., B.S., of Wharfe View, Linton, Wetherby, Yorks.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Tetanus Toxoid after Allergy to A.T.S.

Q.—*Is there any danger in giving tetanus toxoid to a child who has had an allergic reaction to antitoxic serum in the past?*

A.—While no injection should be regarded as completely devoid of risk, the likelihood of reaction in an allergic child is very much less after tetanus toxoid than antitoxic serum. Active immunization is therefore indicated; a cautious course of injections of toxoid should obviate the emergency use of antitoxic serum. It is suggested that a small dose of 0.1 ml. of toxoid should be given deep subcutaneously or intramuscularly, followed by 0.5 ml. or 1.0 ml. about two days later, if the "detector" injection has been trouble-free. With such a mild prophylactic as tetanus toxoid, the remainder of the course can usually follow the accepted scheme—namely, a second full dose after an interval of six weeks, and a third after six to twelve months. Thereafter, periodic boosting is probably necessary every three to five years. When the injections are given, a syringe and adrenaline 1:1,000 must be kept in readiness for the prompt control of any allergic symptoms which may develop. The use of an antihistaminic drug may also be considered.

Allergic children should be actively immunized against diphtheria as well as tetanus. Ideally, a duplicate record card should be given to parents, with instructions that it must be readily available when required.

Impotence in Diabetes

Q.—*Can you tell me what are the aetiology and treatment of impotence in the diabetic?*

A.—Impotence in the male diabetic may occur in the early untreated patient, in which case it is usually temporary and disappears with proper control of the diabetes. Impotence occurring in the treated diabetic tends to be gradual in onset and does not respond to any form of treatment. Its cause is unknown, but it has been suggested that it may be neuropathic or possibly due to local vascular disease; the former seems more probable, as the bulbo-cavernosus reflex is often absent.

Testosterone by injection in large doses may have some slight effect in the early stages, but fails to produce any improvement when impotence is fully established; this condition is therefore not due to lack of male hormone, and the results of testicular biopsy support this view.

Anatomy of Leucotomy

Q.—*Please describe the anatomical extent of the original leucotomies and the present-day modified leucotomies. What tracts are interrupted?*

A.—In the standard prefrontal leucotomy an incision is made in the white matter of the frontal lobe in the plane of the coronal suture. It is carried inferiorly to the floor of the anterior cranial fossa, superolaterally to the cortex of the convexity, and medially to 1 cm. lateral to the midline. The incision divides the nerve fibres connecting all parts of the frontal cortex anterior to it with the medial nucleus of the thalamus. The effects of the operation are decreased by anterior placement of the incision and increased by its posterior placement, the latter carrying the additional risks of motor and trophic disturbances as well as uraemia.

In an attempt to obtain the desired therapeutic effect and limit post-operative personality alteration various modifica-

tions have been introduced. In these the attack is still directed at the thalamo-frontal projections, but is limited in its extent. Thus in bimedial leucotomy the incision is confined to the medial halves of both frontal lobes in the plane described above. In cortical undercutting the cortex on the orbital, supero-lateral, or medial surfaces of the frontal lobes is separated from the underlying white matter. In topectomy areas of frontal cortex are excised (in particular, areas 9 and 10 of Brodman). These procedures are to be considered as allowing of a quantitative reduction in the extent of the leucotomy, there being little evidence as yet that any of the modifications is specific in the treatment of psychoses, neuroses, or intractable pain.

Extra Vitamins and Colds

Q.—*Claims are made that the issue of halibut-liver oil capsules to industrial workers is beneficial in that they prevent upper respiratory tract infections. Is there any evidence that on present-day standards of nutrition this is worth doing?*

A.—There is no reason to believe that the addition of extra vitamin D to a diet which contains an adequate amount of this vitamin will prevent upper respiratory tract infections.

Treatment of Recurrent Boils

Q.—*What is the best treatment for recurrent boils? Have vaccines any place, and, if so, are autogenous any better than stock vaccines?*

A.—The treatment of recurrent boils is the treatment of the cause. The first consideration is the general health, and especially the exclusion of any organic disease such as diabetes or anaemia or any cause of lowered resistance. The second is the exclusion of any source of infection in the patient. This may be a septic focus such as a tooth, or a skin lesion such as flexural eczema or pruritus ani. It is easy to overlook the presence of parasites, since they are uncommon to-day. Thirdly, the environment should come under review. The most important feature here is possible contact with an individual suffering from boils or other sepsis, or with something which such a person handles, including food.

When there is furunculosis pyogenic organisms multiply over the skin of the body, increasing the liability to boils, so that personal hygiene is important; a daily bath followed by a zinc oxide dusting powder and a daily change of underlinen, which is boiled, should be enjoined. If localized, *x*-ray therapy or dry heat and a non-irritating antiseptic lotion such as 1% cetrimide may help. Empirically, the administration of iron and of vitamin B is recommended, cocoa fat and pig fat being avoided. The writer has not used vaccines; those who employ them use autogenous vaccines.

Lead Douches

Q.—*Solutions of lead subacetate have been recommended for douching. What are the chances of the lead being absorbed through the vaginal mucous membrane?*

A.—The vaginal "mucous membrane" is a stratified epithelium similar to that of the skin except that it has no glands and that its keratin layer is thin or absent. Lead salts can be absorbed through the body surface, but not to a significant extent unless they are regularly rubbed into the skin by way of ointments or lotions. Under the latter conditions poisoning has been described, but it is exceptional. Absorption through the vaginal epithelium must be accepted as a possibility, but it is a very remote one when the application is fleeting and superficial, as it would be in the case of douching, and provided the vaginal skin is unbroken. Reference books mention that cases of lead poisoning following prolonged vaginal douching have occurred, but they give no details. One of the difficulties would be to be sure that such poisoning was the result of vaginal absorption rather than the result of transfer of lead to the alimentary or respiratory tracts from the patient's hands, contaminated during the preparation and use of the douche. Provided the usual hygienic precautions are taken to exclude such transfer, douching with lead subacetate would appear to carry a negligible risk.

Dangers of Paraffin Mist

Q.—*A patient of mine uses an apparatus, known as a high-pressure paraffin washer, which squirts a jet of finely divided paraffin on engine parts, etc., for cleaning. Is the inhalation of the finely divided paraffin likely to be harmful? What is the best protection for him?*

A.—No general survey of the health of workers who clean engine parts and castings by spraying them with paraffin under high pressure has yet been carried out. But there is a good deal of evidence that when mineral oils are introduced into the lungs they can set up lipoid or oil pneumonia, and in some cases a generalized fibrosis may develop. The literature on lipoid pneumonia following the use of nasal drops containing mineral oils is extensive, and there has been in this country at least one case (unpublished) in which widespread pulmonary fibrosis was found at necropsy in a man who for about 20 years had been spraying castings with paraffin. Incidentally, when paraffin is ingested, pneumonia may also occur.[1] Some paraffins might contain carcinogenic substances and there is therefore a potential risk of carcinoma of the bronchus or alveoli. In some workers using the mineral-oil spray-gun there have been complaints of dizziness and loss of appetite, and others have contracted dermatitis. In high concentrations the vapours of some paraffins exert a narcotic action on the central nervous system. When the exposure is severe the symptoms may vary from dizziness and unconsciousness to convulsions, but such cases are rare.

The best protective measure would be not to use the spray method at all, because all sprays are notoriously difficult to control. But, unless the work can be done in a booth under efficient exhaust ventilation, the wearing of a respirator fitted with a fresh-air line would prevent inhalation of the atomized oil. The wearing of dust respirators such as the Mark IV or the Microfilter would afford some measure of protection. In addition, protective clothing should be worn and the skin carefully washed daily or at more frequent intervals.

Reference

[1] Gelfand, M. (1949). *British Medical Journal*, 2, 1151.

Correction.—The figures on the abscissa of the graph (Fig. 4) accompanying the article "Maximum Urine Concentration" by Drs. B. E. Miles, A. Paton, and H. E. de Wardener (*Journal*, October 16, p. 901) represent the solute output rate in milliosmols/min., not osmols/min.

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